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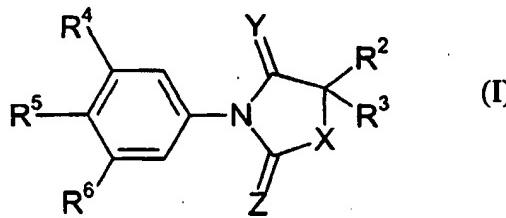
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(54) Title: SMALL MOLECULES USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASE

WO 01/07044 A1



(57) **Abstract:** Novel compounds of formula (I) which are useful for treating or preventing inflammatory and immune cell-mediated diseases. Exemplary compounds are: 5-(*R*)-(4-bromobenzyl)-3-(3-chloro-5-nitrophenyl)-5-methylimidazoline-2,4-dione; and, 5-(*R*)-(4-bromobenzyl)-3-(3-chloro-5-cyanophenyl)-5-methylimidazoline-2,4-dione.

Title of the Invention**SMALL MOLECULES****USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASE**

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Field of the Invention

The present invention relates generally to a series of novel small molecules, their synthesis and their use in the treatment of inflammatory disease.

10 Background of the Invention

Research spanning the last decade has helped to elucidate the molecular events attending cell-cell interactions in the body, especially those events involved in the movement and activation of cells in the immune system. See generally, Springer, T. *Nature*, 1990, 346, 425-434. Cell surface proteins, and especially the Cellular Adhesion Molecules ("CAMs") and "Leukointegrins", including LFA-1, MAC-1 and gp150.95 (referred to in WHO nomenclature as CD18/CD11a, CD18/CD11b, and CD18/CD11c, respectively) have correspondingly been the subject of pharmaceutical research and development having as its goal the intervention in the processes of leukocyte extravasation to sites of injury and leukocyte movement to distinct targets. For example, it is presently believed that prior to 15 the leukocyte extravasation, which is a mandatory component of the inflammatory response, activation of integrins constitutively expressed on leukocytes occurs and is followed by a tight ligand/receptor interaction between integrins (e.g., LFA-1) and one or several distinct intercellular adhesion molecules (ICAMs) designated ICAM-1, ICAM-2, ICAM-3 or ICAM-4 which are expressed on blood vessel endothelial cell surfaces and on 20 other leukocytes. The interaction of the CAMs with the Leukointegrins is a vital step in the normal functioning of the immune system. Immune processes such as antigen presentation, T-cell mediated cytotoxicity and leukocyte extravasation all require cellular adhesion mediated by ICAMs interacting with the Leukointegrins. See generally Kishimoto, T. K.; Rothlein; R. R. *Adv. Pharmacol.* 1994, 25, 117-138 and Diamond, M.; 25 Springer, T. *Current Biology*, 1994, 4, 506-532.

A group of individuals has been identified which lack the appropriate expression of Leukointegrins, a condition termed "Leukocyte Adhesion Deficiency" (Anderson, D. C.; et

al., *Fed. Proc.* 1985, 44, 2671-2677 and Anderson, D. C.; et al., *J. Infect. Dis.* 1985, 152, 668-689). These individuals are unable to mount a normal inflammatory and/or immune response(s) due to an inability of their cells to adhere to cellular substrates. These data show that immune reactions are mitigated when lymphocytes are unable to adhere in a 5 normal fashion due to the lack of functional adhesion molecules of the CD18 family. By virtue of the fact that LAD patients who lack CD18 cannot mount an inflammatory response, it is believed that antagonism of CD18, CD11/ICAM interactions will also inhibit an inflammatory response.

- 10 It has been demonstrated that the antagonism of the interaction between the CAMs and the Leukointegrins can be realized by agents directed against either component. Specifically, blocking of the CAMs, such as for example ICAM-1, or the Leukointegrins, such as for example LFA-1, by antibodies directed against either or both of these molecules effectively inhibits inflammatory responses. *In vitro* models of inflammation and immune 15 response inhibited by antibodies to CAMs or Leukointegrins include antigen or mitogen-induced lymphocyte proliferation, homotypic aggregation of lymphocytes, T-cell mediated cytolysis and antigen-specific induced tolerance. The relevance of the *in vitro* studies are supported by *in vivo* studies with antibodies directed against ICAM-1 or LFA-1. For example, antibodies directed against LFA-1 can prevent thyroid graft rejection and prolong 20 heart allograft survival in mice (Gorski, A.; *Immunology Today*, 1994, 15, 251-255). Of greater significance, antibodies directed against ICAM-1 have shown efficacy *in vivo* as anti-inflammatory agents in human diseases such as renal allograft rejection and rheumatoid arthritis (Rothlein, R. R.; Scharschmidt, L., in: *Adhesion Molecules*; Wegner, C. D., Ed.; 1994, 1-38, Cosimi, C. B.; et al., *J. Immunol.* 1990, 144, 4604-4612 and 25 Kavanaugh, A.; et al., *Arthritis Rheum.* 1994, 37, 992-1004) and antibodies directed against LFA-1 have demonstrated immunosuppressive effects in bone marrow transplantation and in the prevention of early rejection of renal allografts (Fischer, A.; et al., *Lancet*, 1989, 2, 1058-1060 and Le Mauff, B.; et al., *Transplantation*, 1991, 52, 291-295).

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It has also been demonstrated that a recombinant soluble form of ICAM-1 can act as an inhibitor of the ICAM-1 interaction with LFA-1. Soluble ICAM-1 acts as a direct antagonist of CD18,CD11/ICAM-1 interactions on cells and shows inhibitory activity in *in*

vitro models of immune response such as the human mixed lymphocyte response, cytotoxic T cell responses and T cell proliferation from diabetic patients in response to islet cells (Becker, J. C.; *et al.*, *J. Immunol.* 1993, 151, 7224 and Roep, B. O.; *et al.*, *Lancet*, 1994, 343, 1590).

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- Thus, the prior art has demonstrated that large protein molecules which antagonize the binding of the CAMs to the Leukointegrins have therapeutic potential in mitigating inflammatory and immunological responses often associated with the pathogenesis of many autoimmune or inflammatory diseases. However proteins have significant 10 deficiencies as therapeutic agents, including the inability to be delivered orally and potential immunoreactivity which limits the utility of these molecules for chronic administration. Furthermore, protein-based therapeutics are generally expensive to produce.
- 15 Several small molecules have been described in the literature which affect the interaction of CAMs and Leukointegrins. A natural product isolated from the root of *Trichilia rubra* was found to be inhibitory in an *in vitro* cell binding assay (Musza, L. L.; *et al.*, *Tetrahedron*, 1994, 50, 11369-11378). One series of molecules (Boschelli, D. H.; *et al.*, *J. Med. Chem.* 1994, 37, 717 and Boschelli, D. H.; *et al.*, *J. Med. Chem.* 1995, 38, 4597- 20 4614) was found to be orally active in a reverse passive Arthus reaction, an induced model of inflammation that is characterized by neutrophil accumulation (Chang, Y. H.; *et al.*, *Eur. J. Pharmacol.* 1992, 69, 155-164). Another series of molecules was also found to be orally active in a delayed type hypersensitivity reaction in rats (Sanfilippo, P. J.; *et al.*, *J. Med. Chem.* 1995, 38, 1057-1059). All of these molecules appear to act nonspecifically, 25 either by inhibiting the transcription of ICAM-1 along with other proteins or act intracellularly to inhibit the activation of the Leukointegrins by an unknown mechanism. None of the molecules directly antagonize the interaction of the CAMs with the Leukointegrins. Due to lack of potency, lack of selectivity and lack of a specific mechanism of action, the described small molecules are not likely to be satisfactory for 30 therapeutic use.

It follows that small molecules having the similar ability as large protein molecules to directly and selectively antagonize the binding of the CAMs to the Leukointegrins would

make preferable therapeutic agents. WO9839303 discloses a class of small molecule inhibitors of the interaction of LFA-1 and ICAM-1. WO9911258 discloses that the fungal metabolite mevinolin and derivatives bind to LFA-1 and disrupt the interaction of LFA-1 and ICAM-1.

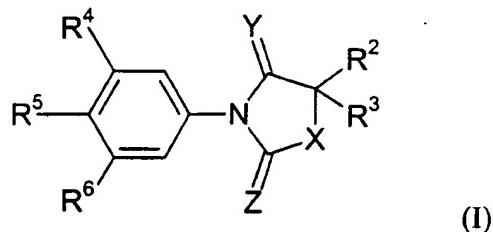
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Summary of the Invention

A first aspect of the invention comprises a method for treating or preventing inflammatory and immune cell-mediated diseases by the administration of certain novel small molecules. 10 These compounds act by inhibiting the interaction of cellular adhesion molecules, specifically by antagonizing the binding of human intercellular adhesion molecules (including ICAM-1, ICAM-2 and ICAM-3) to the Leukointegrins (especially CD18/CD11a). A second aspect of the invention comprises novel small molecules having the above-noted therapeutic activities. A third aspect of the invention comprises methods 15 for making these novel compounds. A final aspect of the invention comprises pharmaceutical compositions comprising the above-mentioned compounds suitable for the prevention or treatment of inflammatory and immune cell-mediated conditions.

Detailed Description of the Invention

20 The invention comprises compounds of the formula I



wherein:

Y is an oxygen or sulfur atom;

Z is an oxygen or sulfur atom;

25 X is a divalent group of the formula $>\text{CHR}^1$, $>\text{NR}^1$, $>\text{CHSO}_2\text{R}^1$, or $>\text{NSO}_2\text{R}^1$, or an oxygen or sulfur atom,

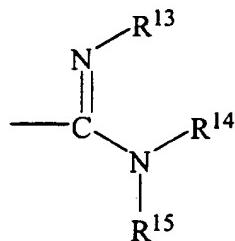
wherein R^1 is:

(A) a hydrogen atom,

- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with:
- (i) halogen,
- (ii) oxo,
- (iii) aryl, which is selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolyzinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, phthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl,
wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
- (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- (e) a group of the formula -COOR⁷, wherein R⁷ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (f) a group of the formula -NR⁸R⁹, wherein R⁸ and R⁹ are each independently a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁸ and R⁹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (g) a group of the formula -CONR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are each independently a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or

wherein R¹⁰ and R¹¹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

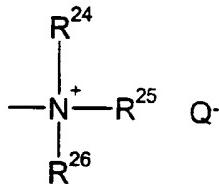
- 5 (h) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (i) a group of the formula -SR^{12b}, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (j) cyano, or
- (k) an amidino group of the formula



10 wherein R¹³, R¹⁴ and R¹⁵ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R¹³, R¹⁴ and R¹⁵ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

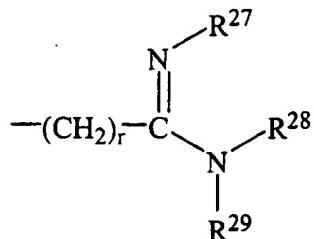
- 15 (iv) a group of the formula -COOR¹⁶, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
- (v) cyano,
- (vi) a group of the formula -CONR¹⁷R¹⁸, wherein R¹⁷ and R¹⁸ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁷ and R¹⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

- (vii) a group of the formula $-OR^{19}$, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (viii) a group of the formula $-SR^{20}$, wherein R²⁰ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- 5 (ix) a group of the formula $-NR^{21}R^{22}$, wherein R²¹ and R²² are each, independently,
 - (a) a hydrogen atom,
 - (b) alkyl or acyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 7 carbon atoms,
 - 10 (c) a group of the formula $-(CH_2)_mCOOH$, wherein m is 0, 1 or 2, or
 - (d) a group of the formula $-(CH_2)_nCOOR^{23}$, wherein n is 0, 1 or 2, wherein R²³ is straight or branched alkyl of 1 to 6 carbon atoms,
- 15 or wherein R²¹ and R²² constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, or
- (x) a quaternary group of the formula



- 20 wherein R²⁴, R²⁵ and R²⁶ are each, independently, a branched or unbranched alkyl group of 1 to 7 carbon atoms and Q⁻ is a chlorine, bromine or iodine counterion,
- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
 - (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
 - 25 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,

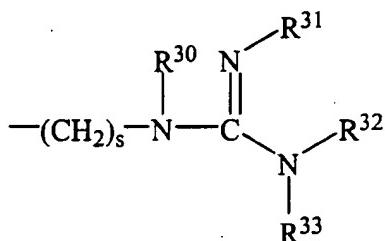
(F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each, independently, a hydrogen atom or alkyl of 1 to 5 carbon atoms, and wherein two of R²⁷, R²⁸ and R²⁹ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

(G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6, and

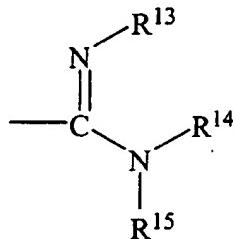
R³⁰, R³¹, R³² and R³³ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R³⁰, R³¹, R³² and R³³ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

(H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

- (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid groups of 1 to 6 carbon atoms, or

- (I) aryl which is selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolyzinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, phthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl, wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
- (i) alkyl of 1 to 3 carbon atoms,
- (ii) -COOH,
- (iii) -SO₂OH,
- (iv) -PO(OH)₂,
- (v) a group of the formula -COOR⁷, wherein R⁷ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (vi) a group of the formula -NR⁸R⁹, wherein R⁸ and R⁹ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁸ and R⁹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (vii) a group of the formula -CONR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁰ and R¹¹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (viii) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (ix) a group of the formula -SR^{12b}, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (x) cyano, or

(xi) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R¹³, R¹⁴ and R¹⁵ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring;

R² is:

- (A) a hydrogen atom, or
- 10 (B) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms wherein said alkyl or cycloalkyl group may optionally be substituted with:
 - (i) a group of the formula -OR³⁴, wherein R³⁴ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
 - 15 (ii) a group of the formula -NR³⁵R³⁶, wherein R³⁵ and R³⁶ are each, independently, a hydrogen atom, alkyl of 1 to 2 carbon atoms, or acyl of 1 to 2 carbon atoms;

R³ is a group of the formula -(CR³⁷R³⁸)_x(CR³⁹R⁴⁰)_yR⁴¹, wherein;

x and y are each independently 0 or 1,

20 R³⁷, R³⁸ and R³⁹ are each, independently:

- (A) a hydrogen atom,
- (B) a group of the formula -OR⁴², wherein R⁴² is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
- (C) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

25 R⁴⁰ is:

- (A) a hydrogen atom,

- (B) a group of the formula $-OR^{42}$, wherein R^{42} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (C) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms, or
- 5 (D) aryl which is selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 10 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 15 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,
- wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
- 20 (i) R^{43} , which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 25 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 30 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,

2-, 3-, 6- or 7-quinoxaliny1, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

5

- (a) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- (e) a group of the formula -COOR⁴⁴, wherein R⁴⁴ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (f) a group of the formula -NR⁴⁵R⁴⁶, wherein R⁴⁵ and R⁴⁶ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁴⁵ and R⁴⁶ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (g) a group of the formula -CONR⁴⁷R⁴⁸, wherein R⁴⁷ and R⁴⁸ are each independently a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁴⁷ and R⁴⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

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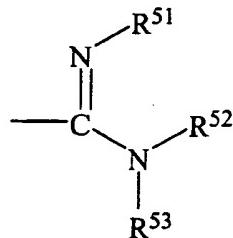
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- (h) a group of the formula $-OR^{49}$, wherein R⁴⁹ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
 - (i) a group of the formula $-SR^{50}$, wherein R⁵⁰ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
 - (j) cyano,
 - (k) nitro,
 - (l) an amidino group of the formula

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wherein R⁵¹, R⁵² and R⁵³ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R⁵¹, R⁵² and R⁵³ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

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- (m) halogen,
- (ii) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁴³,
- (iii) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (iv) a group of the formula $-COOR^{54}$, wherein R⁵⁴ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

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- 5
- (v) a group of the formula $-NR^{55}R^{56}$, wherein R^{55} and R^{56} are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R^{55} and R^{56} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R^{55} and R^{56} may additionally be the group R^{43} ,
 - 10
 - (vi) a group of the formula $-CONR^{57}R^{58}$, wherein R^{57} and R^{58} are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{57} and R^{58} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R^{57} and R^{58} may additionally be the group R^{43} ,
 - 15
 - (vii) a group of the formula $-COR^{59}$, wherein R^{59} is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R^{43} ,
 - (viii) a group of the formula $-OR^{60}$, wherein R^{60} is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R^{43} ,
 - 20
 - (ix) a group of the formula $-SR^{61}$, wherein R^{61} is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R^{43} ,
 - (x) cyano,
 - 25
 - (xi) nitro, or
 - (xii) halogen,

R^{41} is:

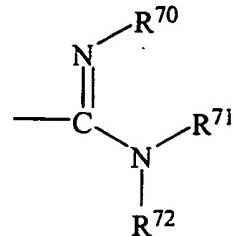
- 30
- aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-

pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl,
2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl,
1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-
oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl,
2-pyrazinyl, 2-triazinyl, 2-, 3-, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-
isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-
benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl,
2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-
isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-
cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6-
or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,
wherein one or more of the hydrogen atoms of said aryl group may
be optionally and independently replaced with:

- (A) R⁶², which is aryl selected from the class consisting of
phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl,
2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-,
2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-,
3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-
imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4-
or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-
pyrazinyl, 2-triazinyl, 2-, 3-, 6- or 7-indolyzinyl, 2-, 3-, 5- or
6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-
benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-
benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-
quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7-
or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl,
2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-,
6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,
wherein one or more of the hydrogen atoms of said aryl
group may be optionally and independently replaced with:
(i) branched or unbranched alkyl of 1 to 6 carbon atoms
or cycloalkyl of 3 to 6 carbon atoms, which alkyl or

- cycloalkyl group may be mono- or polysubstituted
with halogen or oxo,
- (ii) -COOH,
(iii) -SO₂OH,
5 (iv) -PO(OH)₂,
(v) a group of the formula -COOR⁶³, wherein R⁶³ is
straight or branched alkyl of 1 to 5 carbon atoms or
cycloalkyl of 3 to 5 carbon atoms,
10 (vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and
R⁶⁵ are each, independently, a hydrogen atom, alkyl
or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3
to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or
wherein R⁶⁴ and R⁶⁵ constitute a saturated
hydrocarbon bridge of 3 to 5 carbon atoms which
15 together with the nitrogen atom between them form a
heterocyclic ring,
(vii) a group of the formula -CONR⁶⁶R⁶⁷, wherein R⁶⁶
and R⁶⁷ are each, independently, a hydrogen atom,
alkyl or fluoroalkyl of 1 to 6 carbon atoms or
cycloalkyl of 3 to 6 carbon atoms, or wherein R⁶⁶
20 and R⁶⁷ constitute a saturated hydrocarbon bridge of
3 to 5 carbon atoms which together with the nitrogen
atom between them form a heterocyclic ring,
(viii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a
hydrogen atom, or an alkyl, fluoroalkyl or acyl group
25 of 1 to 7 carbon atoms,
(ix) a group of the formula -SR⁶⁹, wherein R⁶⁹ is a
hydrogen atom, or an alkyl, fluoroalkyl or acyl group
of 1 to 7 carbon atoms,
30 (x) cyano,
(xi) nitro, or

(xii) an amidino group of the formula



wherein R⁷⁰, R⁷¹ and R⁷² are each, independently, a hydrogen atom or alkyl or fluoroalkyl of 1 to 3

5 carbon atoms, and wherein two of R⁷⁰, R⁷¹ and R⁷² may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

10

(xiii) halogen,

(B) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁶²,

15

(C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,

(D) a group of the formula -COOR⁷³, wherein R⁷³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

20

(E) a group of the formula -NR⁷⁴R⁷⁵, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁷⁴ and R⁷⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,

25

- 5
- (F) a group of the formula $-CONR^{76}R^{77}$, wherein R^{76} and R^{77} are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{76} and R^{77} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R^{76} and R^{77} may additionally be the group R^{62} ,
- 10 (G) a group of the formula $-COR^{78}$, wherein R^{78} is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R^{62} ,
- (H) a group of the formula $-OR^{79}$, wherein R^{79} is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R^{62} ,
- 15 (I) a group of the formula $-SR^{80}$, wherein R^{80} is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R^{62} ,
- (J) cyano,
- (K) nitro, or
- 20 (L) halogen;
- R^4 is Cl or trifluoromethyl;
- R^5 is a hydrogen, fluorine, chlorine, bromine or iodine atom, methyl or trifluoromethyl; and,
- R^6 is CN or NO_2 ;
- 25 and pharmaceutically acceptable salts thereof.

Preferred are compounds of the formula I

wherein:

- 30 Y is an oxygen or sulfur atom;
- Z is an oxygen or sulfur atom;

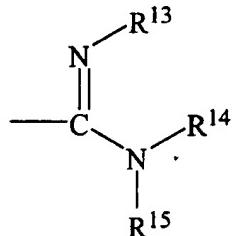
X is a divalent group of the formula $>\text{CHR}^1$, $>\text{NR}^1$, $>\text{CHSO}_2\text{R}^1$, or $>\text{NSO}_2\text{R}^1$, or an oxygen or sulfur atom,

wherein R^1 is:

- (A) a hydrogen atom,
- 5 (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:
 - (i) halogen,
 - (ii) oxo,
 - 10 (iii) aryl selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolyzinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, 15 benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, phthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl,
- 20 wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
 - (a) alkyl of 1 to 3 carbon atoms,
 - (b) -COOH,
 - (c) $-\text{SO}_2\text{OH}$,
 - (d) $-\text{PO}(\text{OH})_2$,
 - (e) a group of the formula $-\text{COOR}^7$, wherein R^7 is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
 - 25 (f) a group of the formula $-\text{NR}^8\text{R}^9$, wherein R^8 and R^9 are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R^8 and R^9 constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together

with the nitrogen atom between them form a heterocyclic ring,

- (g) a group of the formula $-\text{CONR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{10} and R^{11} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (h) a group of the formula $-\text{OR}^{12a}$, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (i) a group of the formula $-\text{SR}^{12b}$, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (j) cyano, or
- (k) an amidino group of the formula

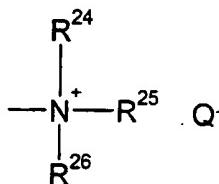


wherein R^{13} , R^{14} and R^{15} are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R^{13} , R^{14} and R^{15} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

- (iv) a group of the formula $-\text{COOR}^{16}$, wherein R^{16} is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
- (v) cyano,
- (vi) a group of the formula $-\text{CONR}^{17}\text{R}^{18}$, wherein R^{17} and R^{18} are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms

or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁷ and R¹⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

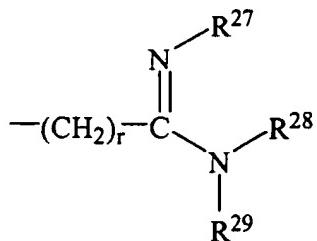
- 5 (vii) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (viii) a group of the formula -SR²⁰, wherein R²⁰ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- 10 (ix) a group of the formula -NR²¹R²², wherein R²¹ and R²² are each, independently:
 - (a) a hydrogen atom,
 - (b) alkyl or acyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 7 carbon atoms,
 - (c) a group of the formula -(CH₂)_mCOOH, wherein m is 0, 1 or 2, or
 - (d) a group of the formula -(CH₂)_nCOOR²³, wherein n is 0, 1 or 2, wherein R²³ is straight or branched alkyl of 1 to 6 carbon atoms,
- 15 or wherein R²¹ and R²² constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, or
- 20 (x) a quaternary group of the formula



wherein R²⁴, R²⁵ and R²⁶ are each, independently, a branched or unbranched alkyl group of 1 to 7 carbon atoms and Q⁻ is a chlorine, bromine or iodine counterion,

- 25 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
- (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,

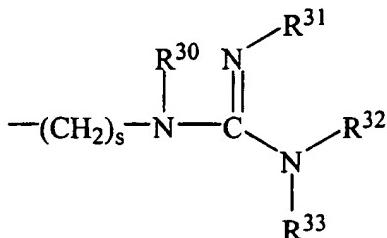
- (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
 (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

5 R^{27} , R^{28} and R^{29} are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R^{27} , R^{28} and R^{29} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

- (G) an guanidino group of the formula



10

wherein s is 2, 3, 4, 5 or 6, and

R^{30} , R^{31} , R^{32} and R^{33} are each independently a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R^{30} , R^{31} , R^{32} and R^{33} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

15

- (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

- 20 (i) alkyl of 1 to 3 carbon atoms,
 (ii) a carboxylic ester group of 2 to 7 carbon atoms,
 (iii) a carboxylic acid group of 2 to 5 carbon atoms,
 (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
 (v) a sulfonic acid group of 1 to 6 carbon atoms;

R² is:

- (A) a hydrogen atom, or
- (B) methyl;

5 R³ is a group of the formula -CH₂R⁴¹, wherein:

R⁴¹ is:

10

aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

20

25

30

(A) R⁶², which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,

quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,

5

wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

10

(i) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,

15

(ii) -COOH,

(iii) -SO₂OH,

(iv) -PO(OH)₂,

(v) a group of the formula -COOR⁶³, wherein R⁶³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

20

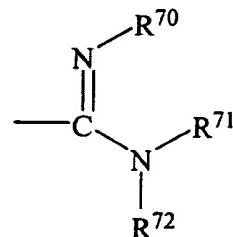
(vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and R⁶⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁶⁴ and R⁶⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

25

(vii) a group of the formula -CONR⁶⁶R⁶⁷, wherein R⁶⁶ and R⁶⁷ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁶⁶ and R⁶⁷ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

30

- 5
- (viii) a group of the formula $-OR^{68}$, wherein R⁶⁸ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
 - (ix) a group of the formula $-SR^{69}$, wherein R⁶⁹ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
 - (x) cyano,
 - (xi) nitro,
 - (xii) an amidino group of the formula



15

wherein R⁷⁰, R⁷¹ and R⁷² are each, independently, a hydrogen atom or alkyl or fluoroalkyl of 1 to 3 carbon atoms, and wherein two of R⁷⁰, R⁷¹ and R⁷² may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

- 20
- (xiii) halogen,
 - (B) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁶²,
 - (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
 - (D) a group of the formula $-COOR^{73}$, wherein R⁷³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- 25

- 5
- (E) a group of the formula $-NR^{74}R^{75}$, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁷⁴ and R⁷⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,
- 10
- (F) a group of the formula $-CONR^{76}R^{77}$, wherein R⁷⁶ and R⁷⁷ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁷⁶ and R⁷⁷ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁶ and R⁷⁷ may additionally be the group R⁶²,
- 15
- (G) a group of the formula $-COR^{78}$, wherein R⁷⁸ is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R⁶²,
- 20
- (H) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,
- 25
- (I) a group of the formula $-SR^{80}$, wherein R⁸⁰ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,
- (J) cyano,
- (K) nitro, or
- (L) halogen;

R⁴ is Cl or trifluoromethyl;

30

R⁵ is a hydrogen, fluorine, chlorine, bromine or iodine atom, methyl or trifluoromethyl; and,

R⁶ is CN or NO₂;
and pharmaceutically acceptable salts thereof.

5 More preferred are compounds of the formula I
wherein:

Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula >CHR¹ or >NR¹,

10 wherein R¹ is:

- (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:

15 (i) oxo,

- (ii) aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl,

20 wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (a) alkyl of 1 to 3 carbon atoms,

- (b) -COOH,

- (c) -SO₂OH,

25 (d) -PO(OH)₂,

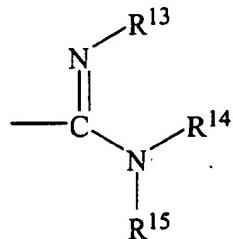
- (e) a group of the formula -COOR⁷, wherein R⁷ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

- (f) a group of the formula -NH₂,

- (g) a group of the formula -CONH₂,

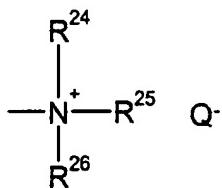
30 (h) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom or a methyl,

- (i) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms,

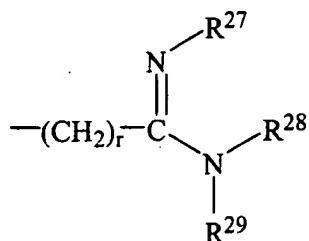
- 5 (j) a group of the formula -COOR¹⁶, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
- (k) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
- (l) a quaternary group of the formula



10

wherein R²⁴, R²⁵ and R²⁶ are each methyl and Q⁻ is a chlorine, bromine or iodine counterion,

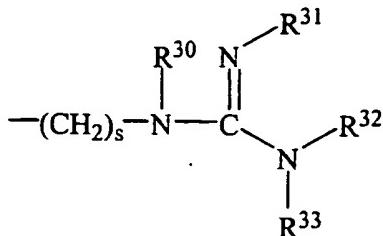
- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
- (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
- 15 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
- (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each hydrogen atoms,

(G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6,

R^{30} , R^{31} , R^{32} and R^{33} are each hydrogen atoms, or

5 (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

- (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- 10 (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid group of 1 to 6 carbon atoms;

R^2 is:

- (A) a hydrogen atom, or
- 15 (B) methyl;

R^3 is a group of the formula $-\text{CH}_2\text{R}^{41}$, wherein

R^{41} is

aryl selected from the class consisting of phenyl, thiophenyl,
20 pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl,
isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl,
thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl,
wherein one or more of the hydrogen atoms of said aryl group are
necessarily and independently replaced with:

- 25 (A) R^{62} , which is aryl selected from the class consisting of
phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl,
oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl,

isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl,

wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

- 5 (i) methyl,
(ii) -COOH,
(iii) -SO₂OH,
(iv) -PO(OH)₂,

- 10 (v) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,
(vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and R⁶⁵ are each, independently, a hydrogen atom or methyl,

- 15 (vii) a group of the formula -CONR⁶⁶R⁶⁷, wherein R⁶⁶ and R⁶⁷ are each, independently, a hydrogen atom or methyl,

- (viii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl,

- (ix) a group of the formula -SR⁶⁹, wherein R⁶⁹ is a hydrogen atom or methyl,

- 20 (x) cyano,
(xi) nitro, or
(xii) halogen,

- 25 (B) methyl, which may be mono- or polysubstituted with fluorine atoms and which additionally may be monosubstituted with R⁶²,

- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,

- 30 (D) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,

- (E) a group of the formula $-NR^{74}R^{75}$, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom or methyl, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,
- 5 (F) a group of the formula $-CONR^{76}R^{77}$, wherein R⁷⁶ and R⁷⁷ are each, independently, a hydrogen atom or methyl, and wherein one of R⁷⁶ and R⁷⁷ may additionally be the group R⁶²,
- 10 (G) a group of the formula $-COR^{78}$, wherein R⁷⁸ is a hydrogen atom, methyl or R⁶²,
- (H) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (I) a group of the formula $-SR^{80}$, wherein R⁸⁰ is a hydrogen atom, methyl or R⁶²,
- 15 (J) cyano,
- (K) nitro, or
- (L) halogen;

R⁴ is Cl or trifluoromethyl;

20 R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

and pharmaceutically acceptable salts thereof.

25 Even more preferred are compounds of the formula I:

wherein:

Y is an oxygen atom;

Z is an oxygen atom;

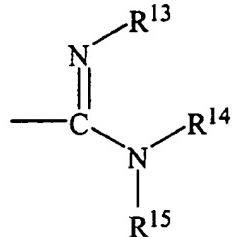
X is a divalent group of the formula >CHR¹ or >NR¹,

30 wherein R¹ is:

- (A) a hydrogen atom,

(B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:

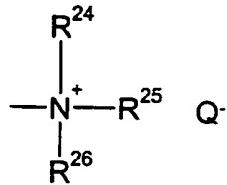
- (i) oxo,
- 5 (ii) aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl, wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
- 10 (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- 15 (e) a group of the formula -COOR⁷, wherein R⁷ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (f) a group of the formula -NH₂,
- (g) a group of the formula -CONH₂,
- 20 (h) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom or a methyl,
- (i) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms,

- 25 (j) a group of the formula -COOR¹⁶, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,

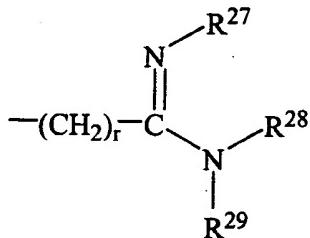
- (k) a group of the formula $-OR^{19}$, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
 (l) a quaternary group of the formula



5

wherein R²⁴, R²⁵ and R²⁶ are each methyl and Q⁻ is a chlorine, bromine or iodine counterion,

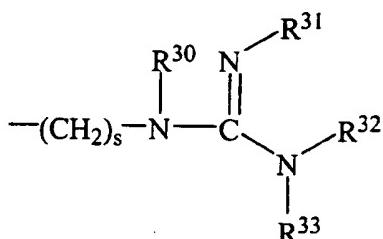
- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
 (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
 10 (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each hydrogen atoms,

- 15 (G) an guanidino group of the formula



15

wherein s is 2, 3, 4, 5 or 6,

R³⁰, R³¹, R³² and R³³ are each hydrogen atoms, or

- (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

20

- (i) alkyl of 1 to 3 carbon atoms,

- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid group of 1 to 6 carbon atoms;

5

 R^2 is:

- (A) a hydrogen atom, or
- (B) methyl;

10 R^3 is a group of the formula $-CH_2R^{41}$, wherein R^{41} is

aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, and pyrazinyl, wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

15

(A) R^{62} , which is aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, and pyrazinyl,

20

wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (i) methyl,
- (ii) $-COOH$,

25

(iii) a group of the formula $-COOR^{63}$, wherein R^{63} is methyl,

(iv) a group of the formula $-OR^{68}$, wherein R^{68} is a hydrogen atom or methyl, or

- (v) halogen,

30

(B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R^{62} ,

- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (D) a group of the formula $-COOR^{73}$, wherein R⁷³ is methyl,
- 5 (E) a group of the formula $-CONR^{76}R^{77}$, wherein R⁷⁶ and R⁷⁷ are each methyl, and wherein one of R⁷⁶ and R⁷⁷ is methyl and the other is the group R⁶²,
- (F) a group of the formula $-COR^{78}$, wherein R⁷⁸ is a hydrogen atom, methyl or R⁶²,
- 10 (G) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (H) cyano,
- (I) nitro, or
- (J) halogen;
- 15

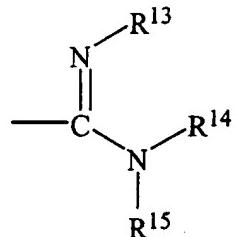
R^4 is Cl or trifluoromethyl;
 R^5 is a hydrogen atom; and,
 R^6 is CN or NO₂;
and pharmaceutically acceptable salts thereof.

20

Still more preferred are compounds of the formula I
wherein:

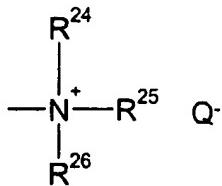
- Y is an oxygen atom;
- 25 Z is an oxygen atom;
- X is a divalent group of the formula $>CHR^1$ or $>NR^1$,
- wherein R¹ is:
- (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:
- 30

- (i) oxo,
- (ii) aryl selected from the class consisting of phenyl or pyridyl,
wherein one or more hydrogen atoms of said aryl group may be
optionally and independently replaced with:
- 5 (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- (e) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen
10 atom or a methyl,
- (f) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms,

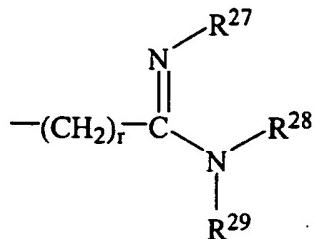
- 15 (iii) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom, or
an alkyl or acyl group of 1 to 7 carbon atoms, or
- (iv) a quaternary group of the formula



wherein R²⁴, R²⁵ and R²⁶ are each methyl and Q⁻ is a chlorine,
bromine or iodine counterion,

- 20 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
(D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
(E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,

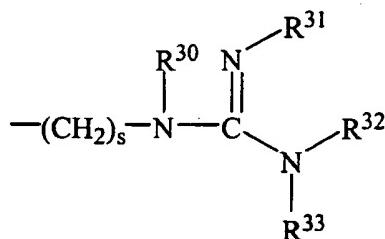
(F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R^{27} , R^{28} and R^{29} are each hydrogen atoms,

5 (G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6,

R^{30} , R^{31} , R^{32} and R^{33} are each hydrogen atoms, or

(H) piperidyl, wherein the nitrogen atom of said group is optionally substituted
10 with:

- (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid group of 1 to 6 carbon atoms;

15 R^2 is:

- (A) a hydrogen atom, or
- (B) methyl;

20

R^3 is a group of the formula $-\text{CH}_2\text{R}^{41}$, wherein

R^{41} is

aryl selected from the class consisting of phenyl or pyridyl,

wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

- (A) R^{62} , which is aryl selected from the class consisting of phenyl, or pyridyl,
5 wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
(i) methyl,
(ii) -COOH
(iii) a group of the formula $-COOR^{63}$, wherein R^{63} is methyl,
10 (iv) a group of the formula $-OR^{68}$, wherein R^{68} is a hydrogen atom or methyl, or
(v) halogen,
(B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R^{62} ,
15 (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with fluorine or oxo,
(D) a group of the formula $-COOR^{73}$, wherein R^{73} is methyl,
20 (E) a group of the formula $-CONR^{76}R^{77}$, wherein R^{76} and R^{77} are each methyl, and wherein one of R^{76} and R^{77} is methyl and the other is the group R^{62} ,
(F) a group of the formula $-COR^{78}$, wherein R^{78} is a hydrogen atom, methyl or R^{62} ,
25 (G) a group of the formula $-OR^{79}$, wherein R^{79} is a hydrogen atom, methyl or R^{62} ,
(H) cyano,
(I) nitro, or
(J) halogen;

30

R^4 is Cl or trifluoromethyl;

R^5 is a hydrogen atom; and,
 R^6 is CN or NO₂;
and pharmaceutically acceptable salts thereof.

5

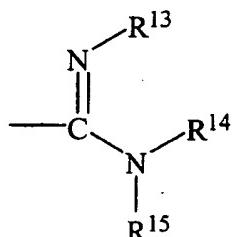
Especially preferred are compounds of the formula I
wherein:

Y is an oxygen atom;
Z is an oxygen atom;

10 X is a divalent group of the formula >CHR¹ or >NR¹,

R^1 is:

- (A) a hydrogen atom,
- (B) alkyl of 1 to 2 carbon atoms which may be monosubstituted with:
 - (i) oxo,
 - (ii) aryl selected from the class consisting of phenyl or pyridyl,
wherein one hydrogen atom of said aryl group may be optionally replaced with:
 - (a) alkyl of 1 to 3 carbon atoms,
 - (b) -COOH,
 - (c) -SO₂OH,
 - (d) -PO(OH)₂,
 - (e) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom or a methyl, or
 - (f) an amidino group of the formula

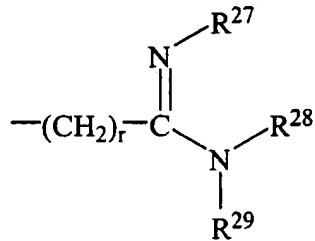


25

wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms, or

(iii) a group of the formula $-OR^{19}$, wherein R¹⁹ is a hydrogen atom or methyl,

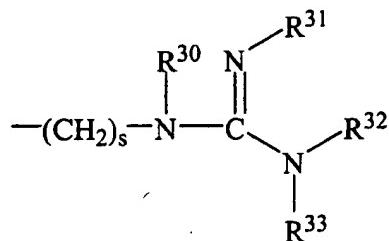
- 5 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
 (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
 (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each hydrogen atoms, or

- 10 (G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6,

R³⁰, R³¹, R³² and R³³ are each hydrogen atoms,

- 15 R² is:

- (A) a hydrogen atom, or
 (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

- 20 R⁴¹ is

phenyl

wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

- (A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl,
wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
- 5 (i) methyl,
- (ii) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,
- (iii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl, or
- 10 (iv) halogen,
- (B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R⁶²,
- (C) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,
- (D) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or
- 15 R⁶²,
- (E) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (F) cyano,
- (G) nitro, or
- 20 (H) halogen;

R⁴ is Cl or trifluoromethyl;

R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

25 and pharmaceutically acceptable salts thereof.

Even more especially preferred are compounds of the formula I
wherein:

30 Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula >NR¹,

R¹ is:

- (A) a hydrogen atom,
- (B) methyl or ethyl, or
- 5 (C) -COCH₃

R² is:

- (A) a hydrogen atom, or
- (B) methyl;

10

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

phenyl

wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

15

- (A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl,
wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
 - (i) methyl,
 - (ii) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,
 - (iii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl, or
 - (iv) halogen,
- 20 (B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R⁶²,
- (C) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,
- (D) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or R⁶²,

25

- (E) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (F) cyano,
- (G) nitro, or
- 5 (H) halogen;

R⁴ is Cl or trifluoromethyl;

R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

10 and pharmaceutically acceptable salts thereof.

Penultimately preferred are compounds of the formula I

wherein:

15 Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula >NR¹,

R¹ is:

- (A) a hydrogen atom,
- 20 (B) methyl or ethyl, or
- (C) -COCH₃

R² is:

- (A) a hydrogen atom, or
- 25 (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

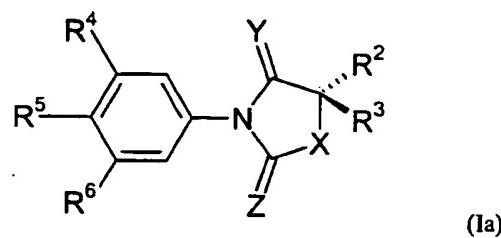
phenyl

30 wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

- (A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
- 5 (i) methyl, or
(ii) halogen,
- (B) methyl, which may be mono- or polysubstituted with fluorine atoms,
- (C) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or
- 10 R⁶²,
- (D) halogen;

R⁴ is a chlorine atom;
R⁵ is a hydrogen atom; and,
15 R⁶ is CN or NO₂;
and pharmaceutically acceptable salts thereof.

- Ultimately preferred are the following compounds of the formula I:
- 20 5-(R)-(4-bromobenzyl)-3-(3-chloro-5-nitrophenyl)-5-methylimidazoline-2,4-dione; and,
5-(R)-(4-bromobenzyl)-3-(3-chloro-5-cyanophenyl)-5-methylimidazoline-2,4-dione;
and pharmaceutically acceptable salts thereof.
- 25 It will be appreciated that the compounds of the formula I have at least one chiral center.
Most preferred are those compounds of formula I with the absolute stereochemistry depicted below in formula Ia.



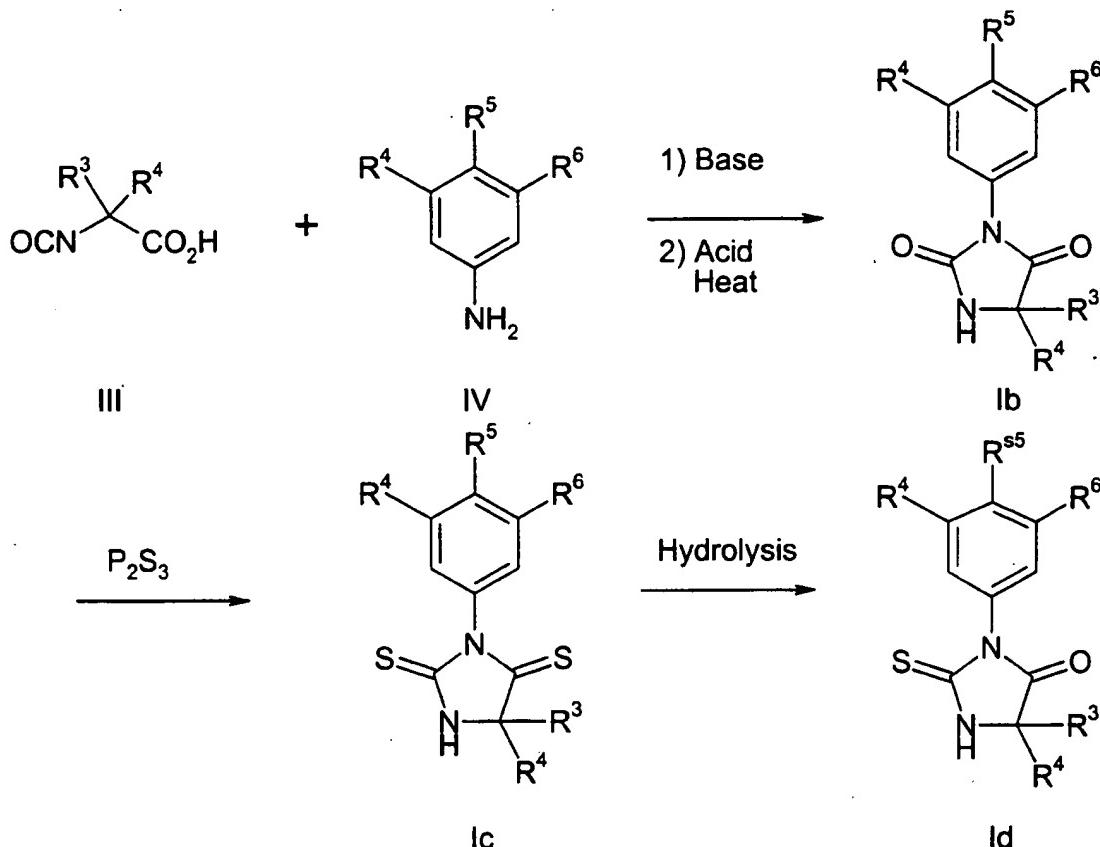
Synthesis of the Compounds of the Invention

5

Compounds of the invention may be prepared by the general methods described below. Typically, reaction progress may be monitored by thin layer chromatography (TLC) if desired. If desired, intermediates and products may be purified by chromatography on silica gel and/or recrystallization. Starting materials and reagents are either commercially available or may be prepared by one skilled in the art using methods described in the chemical literature.

Intermediates used in the preparation of the compounds of formula I may be prepared by the method described below and outlined in Scheme I.

10 15 Scheme I



The isocyanate derivative of the appropriate amino acid (III) is reacted with the desired aniline (IV) in a suitable solvent such as THF plus HMPA , in the presence of a suitable base, such as potassium bis(trimethylsilyl)amide Following workup, consisting of washing with aqueous acid, such as aqueous ammonium chloride followed by purification, for example by silica gel chromatography or recrystallization, the desired Ib is obtained.

If the thiocarbonyl is desired, several reagents are known in the literature which will convert carbonyls to thio carbonyls. A typical sequence involves heating the substrate with a reagent such as P_2S_3 in a high boiling solvent such as tetralin for between 1 and 48 hr. Isolation of the product follows relatively standard conditions such as the dilution of the mixture into an organic solvent such as EtOAc and washing this mixture with water and saturated aqueous NaCl followed by drying and concentration. Purification is accomplished by silica gel chromatography or recrystallization, to afford Ic.

This compound can be selectively hydrolyzed to the desired monothiocarbonyl compound depending on the choice of conditions. In general the thiocarbonyl at the 4-position of the ring is more susceptible to nucleophilic conditions. It can be converted to the 4-oxo-species (Id) by treatment with aqueous ethanolamine followed by acid hydrolysis

5 Purification is easily performed by silica gel chromatography or recrystallization.

Alternatively, the isothiocyanate derivative of the methyl or ethyl ester of III may be reacted with IV in a suitable solvent, such as 1,4-dioxane, under an inert atmosphere at about 50-100 °C for about 1 – 24 hr to provide Id. If one uses the racemic III or ester of

10 III, the product is racemic at the asymmetric carbon. By starting with a single enantiomer of III or ester of III, one obtains the single enantiomer of Id.

The starting amino acids and their derivatives necessary for the synthesis of the hydantoin and thio-hydantoin structures are either commercially available or are produced by obvious

15 modifications of known literature procedures (see e.g.: Williams, R. W. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989, *α-Amino Acid Synthesis*; O'Donnell, M. J., Ed.; Tetrahedron Symposium in Print; Pergamon: London, 1988: Vol. 44, Issue 17, Jung, M. J. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p.227, and Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* 1996, 61: 7398 - 7401). The synthesis and resolution of ethyl 2-amino-2-(4-

20 bromobenzyl)-propanoate is given by way of example.

A solution of alanine ethyl ester hydrochloride (15.3 g, 99.3 mmol) in 60 mL of water was treated with triethylamine (14.6 mL, 104.8 mmol) at room temperature for 30 min. The

25 mixture was then extracted twice with 100 mL of methylene chloride. The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo to afford 10.0 g of the free base of the amino ester (86% yield). The residue was re-dissolved in methylene chloride and cooled in an ice bath. Magnesium sulfate (11.3 g, 93.9 mmol) was added, followed by trimethyl acetaldehyde (9.3 mL, 85.6 mmol). The ice bath was removed, and

30 the mixture was stirred overnight. The magnesium sulfate was removed by filtration, and the filtrate was concentrated in vacuo to afford 11.8 g of the imine intermediate (74.6% yield).

The imine from above (11.8 g, 63.7 mmol) was dissolved in toluene (90 mL). 4-bromobenzyl bromide (17.5 g, 70.1 mmol) was added, and the reaction was cooled to about -10 °C. Potassium tert-butoxide (8.6 g, 76.5 mmol) was added at such a rate that the temperature did not exceed 0 °C. The reaction stirred in the cold bath for two hours, then 5 was diluted with ether and washed with water (150 mL). The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to afford a clear yellow oil. This was treated with 1 N HCl (100 ml, 100 mmol) and stirred overnight. The reaction was extracted with ethyl acetate (100 mL), and the aqueous layer was to afford 14.1 g of the 10 racemic amino ester hydrochloride (68.7% yield). Isocyanate derivatives can be made by reacting the aminoacid ester with a phosgene equivalent such as trichloromethyl chloroformate. This is exemplified in the Synthetic Examples below.

The racemic compounds can be resolved into their component enantiomers via a number of known techniques. Ethyl 2-(*R*)-amino-2-(4-bromobenzyl)-propanoate was produced from 15 racemic ethyl 2-amino-2-(4-bromobenzyl)-propanoate by the following procedure: To 1.3 L of a buffer made from 13.69 g KH₂PO₄ and 2 L of water was added 20 g of the commercially available enzyme Lipase L10 (Amano Enzyme USA Co., Ltd, Lombardi, IL) followed by 12 g of the HCl salt of the racemic amino ester. The pH was monitored and 1 N KOH was added as needed to keep the pH of the mixture at 6.4. The course of the 20 reaction was monitored with reverse phase HPLC and after 2 days, the HPLC analysis indicated that 50.4% of the starting material had been hydrolyzed. At this point enough solid NaHCO₃ was added to adjust the pH to 8.1 and the mixture was extracted twice with toluene, ether and EtOAc. The combined organic layers was dried and concentrated and the crude product purified by silica gel chromatography (EtOAC: Hexanes) to yield 5.21 g 25 (87%) of ethyl 2-(*R*)-amino-2-(4-bromobenzyl)-propanoate.
Modifications to the above procedures and further transformations of initial products to obtain additional compounds of the invention are known to those skilled in the art and are analogous to those described in WO 9839303.

30

Synthetic Examples

Example 1: Synthesis of 5-(*R*)-(4-bromobenzyl)-3-(3-chloro-5-nitrophenyl)-5-methylimidazoline-2,4-dione.

A solution of 0.40 g (5.73 mmol) sodium nitrite in 1 mL H₂O was added dropwise to a
5 stirred suspension of 1.00 g (5.46 mmol) 3,5-dinitroaniline in 5 mL H₂O and 2.5 mL conc. HCl in an ice bath. After 5 min, a solution of 0.70 g (7.10 mmol) copper (I) chloride in 2 mL conc. HCl was added dropwise. About 5 mL of toluene was added and the reaction was allowed to warm to room temperature and then heated 1 hr at 60 °C. The reaction was diluted with water, extracted (4 X EtOAc), washed with H₂O and aqueous Na₂CO₃, dried
10 and concentrated in vacuo to give 1.3 g of a dark oil. Silica gel flash chromatography, eluting with 5% EtOAc-pet ether afforded 1-chloro-3,5-dinitrobenzene (0.86 g, 78%) as a yellow oil.

The above product (0.50 g, 2.47 mmol) was refluxed 1 hr in 6 mL alcohol and 3 mL 20%
15 ammonium sulfide in H₂O. Water was added and the product was filtered, dried and flash chromatographed on silica gel eluting with 10% acetone-pet ether to obtain 3-chloro-5-nitroaniline (0.36 g, 84%) as an orange powder.

Trichloromethylchloroformate (0.233 mL, 1.93 mmol) was added to a two phase mixture
20 of 50 mL aqueous NaHCO₃ and 1.00 g (3.68 mmol) of (*R*)- α -methyl-4-bromophenylalanine methyl ester in 50 mL CH₂Cl₂ at 0 °C. After stirring 10 min in the cold, the phases were separated and the aqueous phase was extracted 3X more with CH₂Cl₂. The combined organic phase was dried, concentrated in vacuo to a semisolid, re-dissolved in CH₂Cl₂, filtered through silica gel, and concentrated again to 0.62 g (56%) oil
25 as the pure isocyanate.

A solution of 1.1 mL (0.55 mmol) of 0.5 M potassium bis(trimethylsilyl)amide in toluene was added to a solution of 0.095 g (0.55 mmol) 3-chloro-5-nitroaniline in 5 mL dry THF and 0.25 mL HMPA in a flame-dried flask under argon in a dry ice-alcohol bath. After
30 stirring 5 min, a solution of the isocyanate (0.164 g, 0.55 mmol) in 1.5 mL THF was added dropwise over 10 min and stirred for another 0.5 hr in the cold. Aqueous NH₄Cl was added which was then extracted 4X with ether, dried and concentrated in vacuo to an oil. The crude product was purified on Analtech 2 mm prep plates, developed in 20% acetone-

pet ether, and isolated and developed again on another plate in 5% EtOAc- CH₂Cl₂ to afford 60.6 mg (25%) of the title compound as a sticky resin.

5 **Example 2: Synthesis of 5-(R)-(4-bromobenzyl)-3-(3-chloro-5-cyanophenyl)-5-methylimidazoline-2,4-dione.**

5-(R)-(4-bromobenzyl)-3-(5-acetamino-3-chlorophenyl)-5-methylimidazoline-2,4-dione (prepared by the process described in Example 1 from the isocyanate derivative of (R)- α -methyl-4-bromophenylalanine methyl ester and 5-acetamino-3-chloroaniline) was hydrolyzed by heating in 2N HCl to give 5-(R)-(4-bromobenzyl)-3-(5-amino-3-chlorophenyl)-5-methylimidazoline-2,4-dione. Sandmeyer reaction with NaNO₂, CuCN and KCN provided the title compound as a resin.

15

Description of Biological Properties

The biological properties of representative compounds of the formula I were investigated by way of the experimental protocol described below.

20

Assay to Determine Inhibition of LFA-1 Binding to ICAM-1

Purpose of Assay:

This assay protocol is designed to study the direct antagonism, by a test compound, of the interaction of the CAM, ICAM-1 with the Leukointegrin CD18/CD11a (LFA-1).

Description of Assay Protocol:

LFA-1 is immunopurified using the TS2/4 antibody from a 20 g pellet of human JY or SKW3 cells, utilizing a protocol previously described (Dustin, M. J.; *et al.*, *J. Immunol.* 1992, 148, 2654-2660). The LFA-1 is purified from SKW3 lysates by immunoaffinity chromatography on TS2/4 LFA-1 mAb Sepharose and eluted at pH 11.5 in the presence of 2 mM MgCl₂ and 1% octylglucoside. After collection and neutralization of fractions from the TS2/4 column, samples are pooled and precleared with Protein G agarose.

A soluble form of ICAM-1 is constructed, expressed, purified and characterized as previously described (Marlin, S.; *et al.*, *Nature*, 1990, 344, 70-72 and see Artuda, A.; *et al.*, *Antimicrob. Agents Chemother.* 1992, 36, 1186-1192). Briefly, isoleucine 454 which is
5 located at the putative boundary between domain 5 of the ectodomain and the transmembrane domain, is changed to a stop codon using standard oligonucleotide-directed mutagenesis. This construction yields a molecule identical with the first 453 amino acids of membrane bound ICAM-1. An expression vector is created with a hamster dihydrofolate reductase gene, a neomycin-resistance marker, and the coding region of the
10 sICAM-1 construct described above, along with the promoter, splice signals, and polyadenylation signal of the SV40 early region. The recombinant plasmid is transfected into CHO DUX cells using standard calcium phosphate methods. Cells are passaged in selective media (G418) and colonies secreting sICAM-1 are amplified using methotrexate. sICAM-1 is purified from serum-free media using traditional non-affinity chromatographic
15 techniques, including ion exchange and size exclusion chromatography.

LFA-1 binding to ICAM-1 is monitored by first incubating sICAM-1 at 40 µg/mL in Dulbecco's phosphate buffered saline with calcium and magnesium, additional 2 mM MgCl₂ and 0.1 mM PMSF (Diluting Buffer) in a 96-well plate for 30 min at room
20 temperature. Plates are then blocked by the addition of 2% (w/v) bovine serum albumin in Diluting Buffer for 37 °C for 1 h. Blocking solution is removed from wells, and test compounds are diluted and then added followed by the addition of approximately 25 ng of immunoaffinity purified LFA-1. The LFA-1 is incubated in the presence of test compound and ICAM-1 at 37 °C for 1 h. Wells are washed 3 times with Diluting Buffer. The bound
25 LFA-1 is detected by the addition of a polyclonal antibody directed against a peptide corresponding to the CD18 cytoplasmic tail in a 1:100 dilution with Diluting Buffer and 1% BSA and allowed to incubate for 45 min at 37 °C. Wells are washed 3 times with Diluting Buffer and the bound polyclonal antibody is detected by the addition of a 1:4000 dilution of horse radish peroxidase conjugated to goat immunoglobulin directed against
30 rabbit immunoglobulin. This reagent is allowed to incubate for 20 min at 37 °C, wells are washed as above and the substrate for the horse radish peroxidase is added to each well to develop a quantitative colorimetric signal proportional to the amount of LFA-1 bound to

sICAM-1. Soluble ICAM-1 (60 µg/mL) is used as a positive control for inhibition of the LFA-1/ICAM-1 interaction. The lack of the addition of LFA-1 to the binding assay is used as a background control for all samples. A dose-response curve is obtained for all test compounds.

5

All compounds made in the above examples were tested in this assay and each found to have a $K_d < 10 \mu\text{M}$.

10

Description of Therapeutic Use

The novel small molecules of formula I provided by the invention inhibit the ICAM-1/LFA-1 dependent homotypic aggregation of human lymphocytes and human lymphocyte adherence to ICAM-1. These compounds have therapeutic utility in the modulation of 15 immune cell activation/proliferation, e.g., as competitive inhibitors of intercellular ligand/receptor binding reactions involving CAMs and Leukointegrins. To be more specific, the compounds of the invention may be used to treat certain inflammatory conditions, including conditions resulting from a response of the non-specific immune system in a mammal (e.g., adult respiratory distress syndrome, shock, oxygen toxicity, 20 multiple organ injury syndrome secondary to septicemia, multiple organ injury syndrome secondary to trauma, reperfusion injury of tissue due to cardiopulmonary bypass, myocardial infarction or use with thrombolysis agents, acute glomerulonephritis, vasculitis, reactive arthritis, dermatosis with acute inflammatory components, stroke, thermal injury, hemodialysis, leukapheresis, ulcerative colitis, necrotizing enterocolitis and granulocyte 25 transfusion associated syndrome) and conditions resulting from a response of the specific immune system in a mammal (e.g., psoriasis, organ/tissue transplant rejection, graft vs. host reactions and autoimmune diseases including Raynaud's syndrome, autoimmune thyroiditis, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, inflammatory bowel disease including Crohn's disease and ulcerative 30 colitis, and systemic lupus erythematosus). The compounds of the invention may also be used in treating asthma or as an adjunct to minimize toxicity with cytokine therapy in the treatment of cancers. In general these compounds may be employed in the treatment of those diseases currently treatable through steroid therapy.

Thus, another aspect of the invention is the provision of a method for the treatment or prophylaxis of the above-described conditions through the administration of therapeutic or prophylactic amounts of one or more compounds of the formula I.

5

- In accordance with the method provided by the invention, the novel compounds of formula I may be administered for either a "prophylactic" or "therapeutic" purpose either alone or with other immunosuppressive or antiinflammatory agents. When provided prophylactically, the immunosuppressive compound(s) are provided in advance of any inflammatory response or symptom (for example, prior to, at, or shortly after the time of an organ or tissue transplant but in advance of any symptoms of organ rejection). The prophylactic administration of a compound of the formula I serves to prevent or attenuate any subsequent inflammatory response (such as, for example, rejection of a transplanted organ or tissue, etc.). The therapeutic administration of a compound of the formula I serves to attenuate any actual inflammation (such as, for example, the rejection of a transplanted organ or tissue). Thus, in accordance with the invention, a compound of the formula I can be administered either prior to the onset of inflammation (so as to suppress an anticipated inflammation) or after the initiation of inflammation.
- 10 The novel compounds of the formula I may, in accordance with the invention, be administered in single or divided doses by the oral, parenteral or topical routes. A suitable oral dosage for a compound of formula I would be in the range of about 0.1 mg to 10 g per day. In parenteral formulations, a suitable dosage unit may contain from 0.1 to 250 mg of said compounds, whereas for topical administration, formulations containing 0.01 to 1%
- 15 active ingredient are preferred. It should be understood, however, that the dosage administration from patient to patient will vary and the dosage for any particular patient will depend upon the clinician's judgement, who will use as criteria for fixing a proper dosage the size and condition of the patient as well as the patient's response to the drug.
- 20 When the compounds of the present invention are to be administered by the oral route, they may be administered as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. Such carrier material can be an inert organic or inorganic carrier material suitable for oral
- 25
- 30

administration. Examples of such carrier materials are water, gelatin, talc, starch, magnesium stearate, gum arabic, vegetable oils, polyalkylene-glycols, petroleum jelly and the like.

- 5 The pharmaceutical preparations can be prepared in a conventional manner and finished dosage forms can be solid dosage forms, for example, tablets, dragees, capsules, and the like, or liquid dosage forms, for example solutions, suspensions, emulsions and the like. The pharmaceutical preparations may be subjected to conventional pharmaceutical operations such as sterilization. Further, the pharmaceutical preparations may contain
10 conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavor-improvers, wetting agents, buffers, salts for varying the osmotic pressure and the like. Solid carrier material which can be used include, for example, starch, lactose, mannitol, methyl cellulose, microcrystalline cellulose, talc, silica, dibasic calcium phosphate, and high molecular weight polymers (such as polyethylene glycol).

15

- For parenteral use, a compound of formula I can be administered in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable oil or a mixture of liquids, which may contain bacteriostatic agents, antioxidants, preservatives, buffers or other solutes to render the solution isotonic with the blood, thickening agents, suspending
20 agents or other pharmaceutically acceptable additives. Additives of this type include, for example, tartrate, citrate and acetate buffers, ethanol, propylene glycol, polyethylene glycol, complex formers (such as EDTA), antioxidants (such as sodium bisulfite, sodium metabisulfite, and ascorbic acid), high molecular weight polymers (such as liquid polyethylene oxides) for viscosity regulation and polyethylene derivatives of sorbitol
25 anhydrides. Preservatives may also be added if necessary, such as benzoic acid, methyl or propyl paraben, benzalkonium chloride and other quaternary ammonium compounds.

- The compounds of this invention may also be administered as solutions for nasal application and may contain in addition to the compounds of this invention suitable
30 buffers, tonicity adjusters, microbial preservatives, antioxidants and viscosity-increasing agents in an aqueous vehicle. Examples of agents used to increase viscosity are polyvinyl alcohol, cellulose derivatives, polyvinylpyrrolidone, polysorbates or glycerin. Microbial

preservatives added may include benzalkonium chloride, thimerosal, chloro-butanol or phenylethyl alcohol.

Additionally, the compounds provided by the invention can be administered by
5 suppository.

Formulations

Compounds of the formula I can be formulated for therapeutic administration in a number
10 of ways. Descriptions of several exemplary formulations are given below.

Example A

Capsules or Tablets

Example A-1		Example A-2	
Ingredients	Quantity	Ingredients	Quantity
Compound of formula I	250 mg	Compound of formula I	50 mg
Starch	160 mg	Dicalcium Phosphate	160 mg
Microcrys. Cellulose	90 mg	Microcrys. Cellulose	90 mg
Sodium Starch Glycolate	10 mg	Stearic acid	5 mg
Magnesium Stearate	2 mg	Sodium Starch Glycolate	10 mg
Fumed colloidal silica	1 mg	Fumed colloidal silica	1 mg

- 5 The compound of formula I is blended into a powder mixture with the premixed excipient materials as identified above with the exception of the lubricant. The lubricant is then blended in and the resulting blend compressed into tablets or filled into hard gelatin capsules.

10

Example B

Parenteral Solutions

Ingredients	Quantity
Compound of formula I	500 mg
PEG 400	40% by volume
Ethyl Alcohol	5% by volume
Saline	55% by volume

- 15 The excipient materials are mixed and then added to one of the compounds of formula I in such volume as is necessary for dissolution. Mixing is continued until the solution is clear. The solution then filtered into the appropriate vials or ampoules and sterilized by autoclaving.

20

Example C

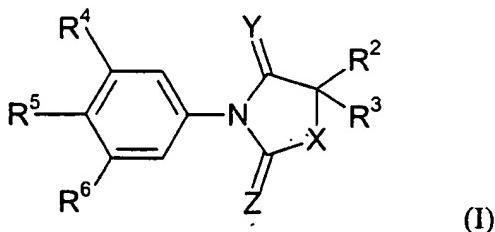
Suspension

Ingredients	Quantity
Compound of formula I	100 mg
Citric acid	1.92g
Benzalkonium chloride	0.025% by weight
EDTA	0.1 % by weight
Polyvinylalcohol	10% by weight
Water	q.s. to 100mL

- 5 The excipient materials are mixed with the water and thereafter one of the compounds of formula I is added and mixing is continued until the suspension is homogeneous. The suspension is then transferred into the appropriate vials or ampoules.

What is claimed is:

1. A compound of the formula I



5 wherein:

Y is an oxygen or sulfur atom;

Z is an oxygen or sulfur atom;

X is a divalent group of the formula $>\text{CHR}^1$, $>\text{NR}^1$, $>\text{CHSO}_2\text{R}^1$, or $>\text{NSO}_2\text{R}^1$, or an oxygen or sulfur atom,

10 wherein R^1 is:

- (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with:

15 (i) halogen,

(ii) oxo,

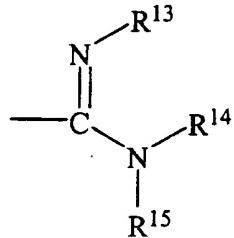
(iii) aryl, which is selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl,

20 oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolizinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, phthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl,

25 wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (a) alkyl of 1 to 3 carbon atoms,
- (b) $-\text{COOH}$,
- (c) $-\text{SO}_2\text{OH}$,

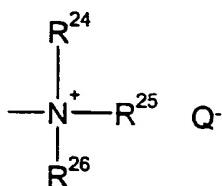
- (d) $-\text{PO}(\text{OH})_2$,
- (e) a group of the formula $-\text{COOR}^7$, wherein R^7 is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- 5 (f) a group of the formula $-\text{NR}^8\text{R}^9$, wherein R^8 and R^9 are each independently a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R^8 and R^9 constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- 10 (g) a group of the formula $-\text{CONR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are each independently a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{10} and R^{11} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- 15 (h) a group of the formula $-\text{OR}^{12a}$, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (i) a group of the formula $-\text{SR}^{12b}$, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- 20 (j) cyano, or
- (k) an amidino group of the formula



25 wherein R¹³, R¹⁴ and R¹⁵ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R¹³, R¹⁴ and R¹⁵ may additionally constitute a

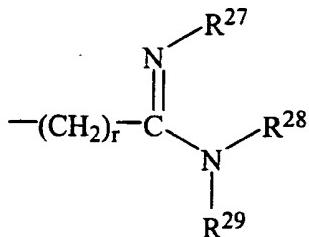
saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

- (iv) a group of the formula $-COOR^{16}$, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
5
- (v) cyano,
- (vi) a group of the formula $-CONR^{17}R^{18}$, wherein R¹⁷ and R¹⁸ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁷ and R¹⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
10
- (vii) a group of the formula $-OR^{19}$, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
15
- (viii) a group of the formula $-SR^{20}$, wherein R²⁰ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (ix) a group of the formula $-NR^{21}R^{22}$, wherein R²¹ and R²² are each, independently,
20
 - (a) a hydrogen atom,
 - (b) alkyl or acyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 7 carbon atoms,
 - (c) a group of the formula $-(CH_2)_mCOOH$, wherein m is 0, 1 or 2, or
 - (d) a group of the formula $-(CH_2)_nCOOR^{23}$, wherein n is 0, 1
25 or 2, wherein R²³ is straight or branched alkyl of 1 to 6 carbon atoms, or wherein R²¹ and R²² constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, or
- (x) a quaternary group of the formula
30



wherein R²⁴, R²⁵ and R²⁶ are each, independently, a branched or unbranched alkyl group of 1 to 7 carbon atoms and Q⁻ is a chlorine, bromine or iodine counterion,

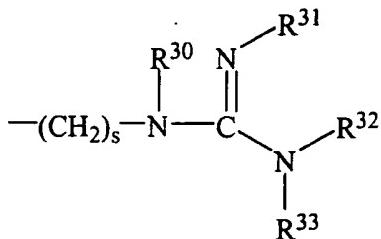
- 5 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
 (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
 (F) an amidino group of the formula



10 wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R²⁷, R²⁸ and R²⁹ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

- 15 (G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6, and

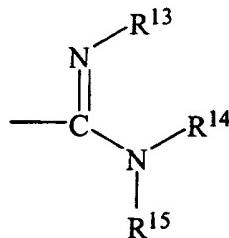
R³⁰, R³¹, R³² and R³³ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R³⁰, R³¹, R³² and R³³ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon

20

- atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,
- (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:
- (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid groups of 1 to 6 carbon atoms, or
- 10 (I) aryl which is selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolizinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, phthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl, wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
- (i) alkyl of 1 to 3 carbon atoms,
- (ii) -COOH,
- (iii) -SO₂OH,
- (iv) -PO(OH)₂,
- (v) a group of the formula -COOR⁷, wherein R⁷ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- 20 (vi) a group of the formula -NR⁸R⁹, wherein R⁸ and R⁹ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁸ and R⁹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- 25 (vii) a group of the formula -CONR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms

or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁰ and R¹¹ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

- 5 (viii) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (ix) a group of the formula -SR^{12b}, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (x) cyano, or
- 10 (xi) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R¹³, R¹⁴ and R¹⁵ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring;

15 R² is:

- (A) a hydrogen atom, or
 - (B) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms wherein said alkyl or cycloalkyl group may optionally be substituted with:
- 20 (i) a group of the formula -OR³⁴, wherein R³⁴ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
 - (ii) a group of the formula -NR³⁵R³⁶, wherein R³⁵ and R³⁶ are each, independently, a hydrogen atom, alkyl of 1 to 2 carbon atoms, or acyl of 1 to 2 carbon atoms;

25 R³ is a group of the formula -(CR³⁷R³⁸)_x(CR³⁹R⁴⁰)_yR⁴¹, wherein:

x and y are each independently 0 or 1,

R³⁷, R³⁸ and R³⁹ are each, independently:

- (A) a hydrogen atom,
- (B) a group of the formula -OR⁴², wherein R⁴² is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
- 5 (C) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

R⁴⁰ is:

- (A) a hydrogen atom,
- (B) a group of the formula -OR⁴², wherein R⁴² is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (C) branched or unbranched alkyl of 1 to 3 carbon atoms or cycloalkyl of 3 to 5 carbon atoms, or
- (D) aryl which is selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolizinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (i) R⁴³, which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-,

3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,
wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

(a) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,

(b) -COOH,

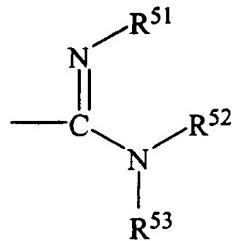
(c) -SO₂OH,

(d) -PO(OH)₂,

(e) a group of the formula -COOR⁴⁴, wherein R⁴⁴ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

(f) a group of the formula -NR⁴⁵R⁴⁶, wherein R⁴⁵ and R⁴⁶ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁴⁵ and R⁴⁶ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

- 5
- (g) a group of the formula $-\text{CONR}^{47}\text{R}^{48}$, wherein R^{47} and R^{48} are each independently a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{47} and R^{48} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- 10
- (h) a group of the formula $-\text{OR}^{49}$, wherein R^{49} is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- (i) a group of the formula $-\text{SR}^{50}$, wherein R^{50} is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- 15
- (j) cyano,
- (k) nitro,
- (l) an amidino group of the formula



- 20
- wherein R^{51} , R^{52} and R^{53} are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms, and wherein two of R^{51} , R^{52} and R^{53} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or
- (m) halogen,

- (ii) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁴³,
- (iii) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (iv) a group of the formula –COOR⁵⁴, wherein R⁵⁴ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (v) a group of the formula –NR⁵⁵R⁵⁶, wherein R⁵⁵ and R⁵⁶ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁵⁵ and R⁵⁶ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁵⁵ and R⁵⁶ may additionally be the group R⁴³,
- (vi) a group of the formula –CONR⁵⁷R⁵⁸, wherein R⁵⁷ and R⁵⁸ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁵⁷ and R⁵⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁵⁷ and R⁵⁸ may additionally be the group R⁴³,
- (vii) a group of the formula –COR⁵⁹, wherein R⁵⁹ is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R⁴³,
- (viii) a group of the formula –OR⁶⁰, wherein R⁶⁰ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁴³,

- 5
- (ix) a group of the formula $-SR^{61}$, wherein R^{61} is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R^{43} ,
 - (x) cyano,
 - (xi) nitro, or
 - (xii) halogen,

R^{41} is:

10

aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

15

(A) R^{62} , which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,

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wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

25

(A) R^{62} , which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,

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wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

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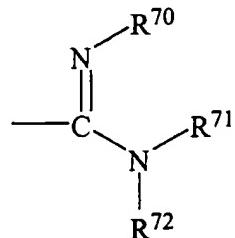
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benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (i) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (ii) -COOH,
- (iii) -SO₂OH,
- (iv) -PO(OH)₂,
- (v) a group of the formula -COOR⁶³, wherein R⁶³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and R⁶⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁶⁴ and R⁶⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- (vii) a group of the formula -CONR⁶⁶R⁶⁷, wherein R⁶⁶ and R⁶⁷ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁶⁶ and R⁶⁷ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

- (viii) a group of the formula $-OR^{68}$, wherein R⁶⁸ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- 5 (ix) a group of the formula $-SR^{69}$, wherein R⁶⁹ is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- (x) cyano,
- (xi) nitro, or
- (xii) an amidino group of the formula



10

wherein R⁷⁰, R⁷¹ and R⁷² are each, independently, a hydrogen atom or alkyl or fluoroalkyl of 1 to 3 carbon atoms, and wherein two of R⁷⁰, R⁷¹ and R⁷² may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

15

- (xii) halogen,

20

- (B) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁶²,

25

- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (D) a group of the formula $-COOR^{73}$, wherein R⁷³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,

- 5
- (E) a group of the formula $-NR^{74}R^{75}$, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁷⁴ and R⁷⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,
- 10
- (F) a group of the formula $-CONR^{76}R^{77}$, wherein R⁷⁶ and R⁷⁷ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁷⁶ and R⁷⁷ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁶ and R⁷⁷ may additionally be the group R⁶²,
- 15
- (G) a group of the formula $-COR^{78}$, wherein R⁷⁸ is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R⁶²,
- 20
- (H) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,
- 25
- (I) a group of the formula $-SR^{80}$, wherein R⁸⁰ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,
- (J) cyano,
- (K) nitro, or
- (L) halogen;

R⁴ is Cl or trifluoromethyl;
30 R⁵ is a hydrogen, fluorine, chlorine, bromine or iodine atom, methyl or trifluoromethyl; and,

R⁶ is CN or NO₂;
or a pharmaceutically acceptable salt thereof.

5 2. A compound of the formula I, in accordance with claim 1, wherein:

Y is an oxygen or sulfur atom;

Z is an oxygen or sulfur atom;

X is a divalent group of the formula >CHR¹, >NR¹, >CHSO₂R¹, or >NSO₂R¹, or an oxygen or sulfur atom,

10 wherein R¹ is:

- (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:

15 (i) halogen,

(ii) oxo,

(iii) aryl selected from the class consisting of phenyl, naphthyl, indolyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, triazinyl, indolyzinyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzthiazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, purinyl, quinolizinyl, cinnolinyl, pthalaninyl, quinoxalinyl, napthyridinyl, pteridinyl and quinazolinyl,

20 wherein one or more hydrogen atoms of said aryl group may be

wherein one or more hydrogen atoms of said aryl group may be
optionally and independently replaced with:

- (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,

30

- 5
- (e) a group of the formula $-COOR^7$, wherein R^7 is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
 - (f) a group of the formula $-NR^8R^9$, wherein R^8 and R^9 are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R^8 and R^9 constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

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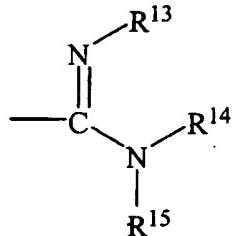
 - (g) a group of the formula $-CONR^{10}R^{11}$, wherein R^{10} and R^{11} are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{10} and R^{11} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,

15

 - (h) a group of the formula $-OR^{12a}$, wherein R^{12a} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
 - (i) a group of the formula $-SR^{12b}$, wherein R^{12b} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,

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 - (j) cyano, or
 - (k) an amidino group of the formula

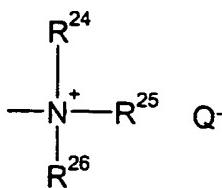


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wherein R^{13} , R^{14} and R^{15} are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R^{13} , R^{14} and R^{15} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which

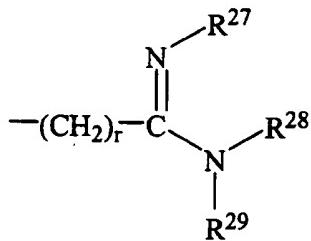
together with the nitrogen atom(s) between them form a heterocyclic ring,

- (iv) a group of the formula $-COOR^{16}$, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
5
- (v) cyano,
- (vi) a group of the formula $-CONR^{17}R^{18}$, wherein R¹⁷ and R¹⁸ are each, independently, a hydrogen atom, alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R¹⁷ and R¹⁸ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms
10 which together with the nitrogen atom between them form a heterocyclic ring,
- (vii) a group of the formula $-OR^{19}$, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
15
- (viii) a group of the formula $-SR^{20}$, wherein R²⁰ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms,
- (ix) a group of the formula $-NR^{21}R^{22}$, wherein R²¹ and R²² are each, independently:
20
 - (a) a hydrogen atom,
 - (b) alkyl or acyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 7 carbon atoms,
 - (c) a group of the formula $-(CH_2)_mCOOH$, wherein m is 0, 1 or 2, or
 - (d) a group of the formula $-(CH_2)_nCOOR^{23}$, wherein n is 0, 1
25 or 2, wherein R²³ is straight or branched alkyl of 1 to 6 carbon atoms, or wherein R²¹ and R²² constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, or
- (x) a quaternary group of the formula
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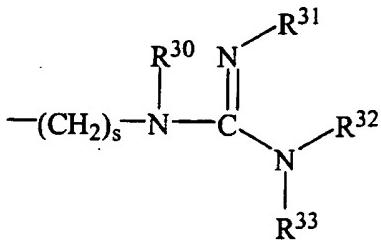
wherein R²⁴, R²⁵ and R²⁶ are each, independently, a branched or unbranched alkyl group of 1 to 7 carbon atoms and Q⁻ is a chlorine, bromine or iodine counterion,

- 5 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
- (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
- (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
- (F) an amidino group of the formula



10 wherein r is 2, 3, 4, 5 or 6, and
 R²⁷, R²⁸ and R²⁹ are each, independently, a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R²⁷, R²⁸ and R²⁹ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring,

- 15 (G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6, and
 R³⁰, R³¹, R³² and R³³ are each independently a hydrogen atom or alkyl of 1 to 3 carbon atoms and wherein two of R³⁰, R³¹, R³² and R³³ may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon

atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

(H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

- 5 (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid group of 1 to 6 carbon atoms;

10 R² is:

- (A) a hydrogen atom, or
- (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein:

15 R⁴¹ is:

aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4- or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolizinyl, 2-, 3-, 5- or 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7- or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl, 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-, 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl, wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

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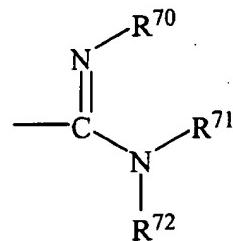
- (A) R⁶², which is aryl selected from the class consisting of phenyl, 2-naphthyl, 2-, 3-, 5- or 6-indolyl, 2- or 3-thiophenyl,

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2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-furyl, 1-,
 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-,
 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 1-, 2-, 4- or 5-
 imidazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-oxadiazolyl, 1-, 4-
 or 5-triazolyl, 2-thiadiazolyl, 3- or 4-pyridazinyl, 2-
 pyrazinyl, 2-triazinyl, 2-, -3, 6- or 7-indolyzinyl, 2-, 3-, 5- or
 6-isoindolyl, 2-, 3-, 5- or 6-benzo[b]furanyl, 2-, 3-, 5- or 6-
 benzo[b]thiophenyl, 3-, 5- or 6-indazolyl, 2-, 5- or 6-
 benzthiazolyl, 2-, 5- or 6-benzimidazolyl, 2-, 3-, 6- or 7-
 quinolinyl, 3-, 6- or 7-isoquinolinyl, 2- or 8-purinyl, 2-, 3-, 7-
 or 8-quinolizinyl, 3-, 6- or 7-cinnolinyl, 6- or 7-phthalaninyl,
 2-, 3-, 6- or 7-quinoxalinyl, 2-, 3-, 6- or 7-naphthyridinyl, 2-,
 6- or 7-pteridinyl and 2-, 6- or 7-quinazolinyl,
 wherein one or more of the hydrogen atoms of said aryl
 group may be optionally and independently replaced with:
 (i) branched or unbranched alkyl of 1 to 6 carbon atoms
 or cycloalkyl of 3 to 6 carbon atoms, which alkyl or
 cycloalkyl group may be mono- or polysubstituted
 with halogen or oxo,
 (ii) -COOH,
 (iii) -SO₂OH,
 (iv) -PO(OH)₂,
 (v) a group of the formula -COOR⁶³, wherein R⁶³ is
 straight or branched alkyl of 1 to 5 carbon atoms or
 cycloalkyl of 3 to 5 carbon atoms,
 (vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and
 R⁶⁵ are each, independently, a hydrogen atom, alkyl
 or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3
 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or
 wherein R⁶⁴ and R⁶⁵ constitute a saturated
 hydrocarbon bridge of 3 to 5 carbon atoms which

together with the nitrogen atom between them form a heterocyclic ring,

- (vii) a group of the formula $-\text{CONR}^{66}\text{R}^{67}$, wherein R^{66} and R^{67} are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R^{66} and R^{67} constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring,
- 10 (viii) a group of the formula $-\text{OR}^{68}$, wherein R^{68} is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- (ix) a group of the formula $-\text{SR}^{69}$, wherein R^{69} is a hydrogen atom, or an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms,
- 15 (x) cyano,
- (xi) nitro,
- (xii) an amidino group of the formula



20 wherein R^{70} , R^{71} and R^{72} are each, independently, a hydrogen atom or alkyl or fluoroalkyl of 1 to 3 carbon atoms, and wherein two of R^{70} , R^{71} and R^{72} may additionally constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom(s) between them form a heterocyclic ring, or

- 25 (xiii) halogen,

- (B) methyl, which may be mono- or polysubstituted with fluorine atoms and additionally may be monosubstituted with R⁶²,
- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (D) a group of the formula -COOR⁷³, wherein R⁷³ is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
- (E) a group of the formula -NR⁷⁴R⁷⁵, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms, cycloalkyl of 3 to 6 carbon atoms or acyl of 1 to 7 carbon atoms, or wherein R⁷⁴ and R⁷⁵ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,
- (F) a group of the formula -CONR⁷⁶R⁷⁷, wherein R⁷⁶ and R⁷⁷ are each, independently, a hydrogen atom, alkyl or fluoroalkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, or wherein R⁷⁶ and R⁷⁷ constitute a saturated hydrocarbon bridge of 3 to 5 carbon atoms which together with the nitrogen atom between them form a heterocyclic ring, and wherein one of R⁷⁶ and R⁷⁷ may additionally be the group R⁶²,
- (G) a group of the formula -COR⁷⁸, wherein R⁷⁸ is a hydrogen atom, straight or branched alkyl of 1 to 5 carbon atoms, cycloalkyl of 3 to 5 carbon atoms or R⁶²,
- (H) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,

- (I) a group of the formula $-SR^{80}$, wherein R⁸⁰ is a hydrogen atom, an alkyl, fluoroalkyl or acyl group of 1 to 7 carbon atoms, or R⁶²,
- 5 (J) cyano,
- (K) nitro, or
- (L) halogen;

R⁴ is Cl or trifluoromethyl;

R⁵ is a hydrogen, fluorine, chlorine, bromine or iodine atom, methyl or trifluoromethyl; and,

10 R⁶ is CN or NO₂;

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula I, in accordance with claim 1, wherein:

15 Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula >CHR¹ or >NR¹,

wherein R¹ is:

(A) a hydrogen atom,

20 (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:

(i) oxo,

(ii) aryl selected from the class consisting of phenyl, thiophenyl,

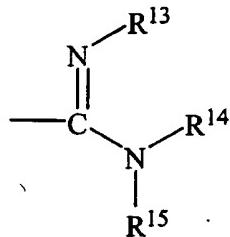
25 pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl, wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:

30 (a) alkyl of 1 to 3 carbon atoms,

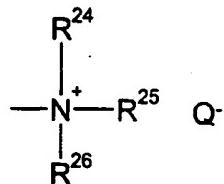
(b) -COOH,

(c) -SO₂OH,

- 5
- (d) $-\text{PO}(\text{OH})_2$,
 - (e) a group of the formula $-\text{COOR}^7$, wherein R^7 is straight or branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5 carbon atoms,
 - (f) a group of the formula $-\text{NH}_2$,
 - (g) a group of the formula $-\text{CONH}_2$,
 - (h) a group of the formula $-\text{OR}^{12a}$, wherein R^{12a} is a hydrogen atom or a methyl,
 - (i) an amidino group of the formula



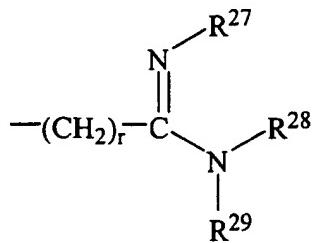
- wherein R^{13} , R^{14} and R^{15} are each hydrogen atoms,
- (j) a group of the formula $-\text{COOR}^{16}$, wherein R^{16} is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
 - (k) a group of the formula $-\text{OR}^{19}$, wherein R^{19} is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
 - (l) a quaternary group of the formula



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wherein R^{24} , R^{25} and R^{26} are each methyl and Q^- is a chlorine, bromine or iodine counterion,

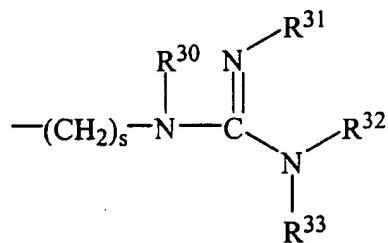
- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
- (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
- (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
- (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R^{27} , R^{28} and R^{29} are each hydrogen atoms,

- (G) an guanidino group of the formula



5

wherein s is 2, 3, 4, 5 or 6,

R^{30} , R^{31} , R^{32} and R^{33} are each hydrogen atoms, or

- (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

10 (i) alkyl of 1 to 3 carbon atoms,

(ii) a carboxylic ester group of 2 to 7 carbon atoms,

(iii) a carboxylic acid group of 2 to 5 carbon atoms,

(iv) a phosphonic acid group of 1 to 6 carbon atoms, or

(v) a sulfonic acid group of 1 to 6 carbon atoms;

15

R^2 is:

- (A) a hydrogen atom, or

- (B) methyl;

20 R^3 is a group of the formula $-\text{CH}_2\text{R}^{41}$, wherein

R^{41} is

aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl,

isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl, wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

- 5 (A) R⁶², which is aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl, wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
- 10 (i) methyl,
(ii) -COOH,
(iii) -SO₂OH,
15 (iv) -PO(OH)₂,
(v) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,
(vi) a group of the formula -NR⁶⁴R⁶⁵, wherein R⁶⁴ and R⁶⁵ are each, independently, a hydrogen atom or methyl,
20 (vii) a group of the formula -CONR⁶⁶R⁶⁷, wherein R⁶⁶ and R⁶⁷ are each, independently, a hydrogen atom or methyl,
(viii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl,
25 (ix) a group of the formula -SR⁶⁹, wherein R⁶⁹ is a hydrogen atom or methyl,
(x) cyano,
(xi) nitro, or
30 (xii) halogen,

- (B) methyl, which may be mono- or polysubstituted with fluorine atoms and which additionally may be monosubstituted with R⁶²,
- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- (D) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,
- (E) a group of the formula -NR⁷⁴R⁷⁵, wherein R⁷⁴ and R⁷⁵ are each, independently, a hydrogen atom or methyl, and wherein one of R⁷⁴ and R⁷⁵ may additionally be the group R⁶²,
- (F) a group of the formula -CONR⁷⁶R⁷⁷, wherein R⁷⁶ and R⁷⁷ are each, independently, a hydrogen atom or methyl, and wherein one of R⁷⁶ and R⁷⁷ may additionally be the group R⁶²,
- (G) a group of the formula -COR⁷⁸, wherein R⁷⁸ is a hydrogen atom, methyl or R⁶²,
- (H) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (I) a group of the formula -SR⁸⁰, wherein R⁸⁰ is a hydrogen atom, methyl or R⁶²,
- (J) cyano,
- (K) nitro, or
- (L) halogen;

25

R⁴ is Cl or trifluoromethyl;

R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

or a pharmaceutically acceptable salt thereof.

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4. A compound of the formula I, in accordance with claim 1, wherein:

Y is an oxygen atom;

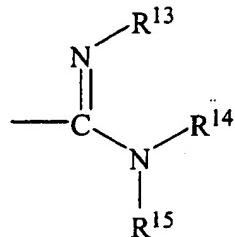
Z is an oxygen atom;

X is a divalent group of the formula $>\text{CHR}^1$ or $>\text{NR}^1$,

wherein R¹ is:

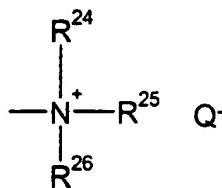
- 5 (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6
 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted
 with:
- 10 (i) oxo,
- (ii) aryl selected from the class consisting of phenyl, thiophenyl,
 pyridyl, pyrimidinyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl,
 isoxazolyl, imidazolyl, isothiazolyl, oxadiazolyl, triazolyl,
 thiadiazolyl, pyridazinyl, pyrazinyl and triazinyl,
 wherein one or more hydrogen atoms of said aryl group may be
15 optionally and independently replaced with:
- (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- 20 (e) a group of the formula -COOR⁷, wherein R⁷ is straight or
 branched alkyl of 1 to 5 carbon atoms or cycloalkyl of 3 to 5
 carbon atoms,
- (f) a group of the formula -NH₂,
- (g) a group of the formula -CONH₂,
- 25 (h) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen
 atom or a methyl,

- (i) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms,

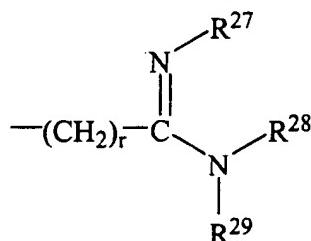
- 5 (j) a group of the formula -COOR¹⁶, wherein R¹⁶ is straight or branched alkyl of 1 to 7 carbon atoms or cycloalkyl of 3 to 6 carbon atoms,
 (k) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
 (l) a quaternary group of the formula



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wherein R²⁴, R²⁵ and R²⁶ are each methyl and Q⁻ is a chlorine, bromine or iodine counterion,

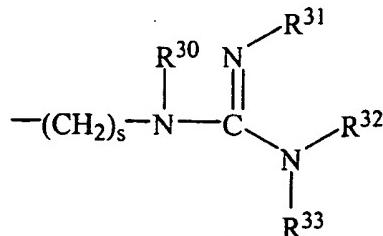
- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
 (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
 15 (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
 (F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each hydrogen atoms,

(G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6,

R³⁰, R³¹, R³² and R³³ are each hydrogen atoms, or

5 (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted with:

- (i) alkyl of 1 to 3 carbon atoms,
- (ii) a carboxylic ester group of 2 to 7 carbon atoms,
- (iii) a carboxylic acid group of 2 to 5 carbon atoms,
- 10 (iv) a phosphonic acid group of 1 to 6 carbon atoms, or
- (v) a sulfonic acid group of 1 to 6 carbon atoms;

R² is:

- 15 (A) a hydrogen atom, or
- (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

20 aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, and pyrazinyl, wherein one or more of the hydrogen atoms of said aryl group are necessarily and independently replaced with:

- 25 (A) R⁶², which is aryl selected from the class consisting of phenyl, thiophenyl, pyridyl, pyrimidinyl, furyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, and pyrazinyl,

wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

- (i) methyl,
- (ii) -COOH,
- 5 (iii) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,
- (iv) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl, or
- (v) halogen,

- 10 (B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R⁶²,
- (C) branched or unbranched alkyl of 2 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be mono- or polysubstituted with halogen or oxo,
- 15 (D) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,
- (E) a group of the formula -CONR⁷⁶R⁷⁷, wherein R⁷⁶ and R⁷⁷ are each methyl, and wherein one of R⁷⁶ and R⁷⁷ is methyl and the other is the group R⁶²,
- (F) a group of the formula -COR⁷⁸, wherein R⁷⁸ is a hydrogen atom, methyl or R⁶²,
- 20 (G) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (H) cyano,
- (I) nitro, or
- 25 (J) halogen;

R⁴ is Cl or trifluoromethyl;

R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

30 or a pharmaceutically acceptable salt thereof.

5. A compound of the formula I, in accordance with claim 1, wherein:

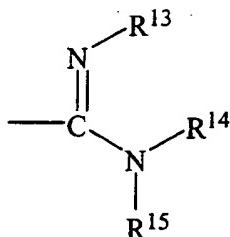
Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula $>\text{CHR}^1$ or $>\text{NR}^1$,

wherein R¹ is:

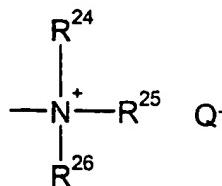
- 5 (A) a hydrogen atom,
- (B) branched or unbranched alkyl of 1 to 6 carbon atoms or cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl group may be monosubstituted with:
 - (i) oxo,
 - 10 (ii) aryl selected from the class consisting of phenyl or pyridyl, wherein one or more hydrogen atoms of said aryl group may be optionally and independently replaced with:
 - (a) alkyl of 1 to 3 carbon atoms,
 - (b) -COOH,
 - 15 (c) -SO₂OH,
 - (d) -PO(OH)₂,
 - (e) a group of the formula -OR^{12a}, wherein R^{12a} is a hydrogen atom or a methyl,
 - (f) an amidino group of the formula



20

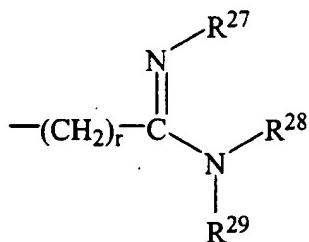
wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms,

- (iii) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom, or an alkyl or acyl group of 1 to 7 carbon atoms, or
- (iv) a quaternary group of the formula



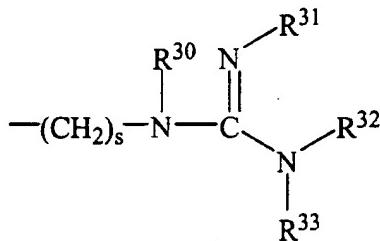
wherein R²⁴, R²⁵ and R²⁶ are each methyl and Q⁻ is a chlorine, bromine or iodine counterion,

- 5 (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
(D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
(E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
(F) an amidino group of the formula



wherein r is 2, 3, 4, 5 or 6, and

- 10 R²⁷, R²⁸ and R²⁹ are each hydrogen atoms,
(G) an guanidino group of the formula



wherein s is 2, 3, 4, 5 or 6,

R^{30} , R^{31} , R^{32} and R^{33} are each hydrogen atoms, or

- 15 (H) piperidyl, wherein the nitrogen atom of said group is optionally substituted
with:

 - (i) alkyl of 1 to 3 carbon atoms,
 - (ii) a carboxylic ester group of 2 to 7 carbon atoms,
 - (iii) a carboxylic acid group of 2 to 5 carbon atoms,
 - 20 (iv) a phosphonic acid group of 1 to 6 carbon atoms, or

(v) a sulfonic acid group of 1 to 6 carbon atoms;

R² is:

- 5 (A) a hydrogen atom, or
 (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

10 aryl selected from the class consisting of phenyl or pyridyl,
 wherein one or more of the hydrogen atoms of said aryl group are
 necessarily and independently replaced with:

15

- (A) R⁶², which is aryl selected from the class consisting of
 phenyl, or pyridyl,

 wherein one or more of the hydrogen atoms of said aryl
 group may be optionally and independently replaced with:

(i) methyl,

(ii) -COOH

(iii) a group of the formula -COOR⁶³, wherein R⁶³ is
 methyl,

20

(iv) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a
 hydrogen atom or methyl, or

(v) halogen,

- (B) methyl, which may be mono- or polysubstituted with

fluorine atoms or which may be monosubstituted with R⁶²,

25

(C) branched or unbranched alkyl of 2 to 6 carbon atoms or
 cycloalkyl of 3 to 6 carbon atoms, which alkyl or cycloalkyl
 group may be mono- or polysubstituted with fluorine or oxo,

(D) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,

30

(E) a group of the formula -CONR⁷⁶R⁷⁷, wherein R⁷⁶ and R⁷⁷
 are each methyl, and wherein one of R⁷⁶ and R⁷⁷ is methyl
 and the other is the group R⁶²,

- (F) a group of the formula $-COR^{78}$, wherein R⁷⁸ is a hydrogen atom, methyl or R⁶²,
- (G) a group of the formula $-OR^{79}$, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- 5 (H) cyano,
- (I) nitro, or
- (J) halogen;

R⁴ is Cl or trifluoromethyl;

10 R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

or a pharmaceutically acceptable salt thereof.

15 6. A compound of the formula I, in accordance with claim 1, wherein:

Y is an oxygen atom;

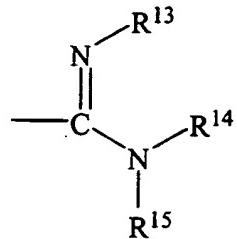
Z is an oxygen atom;

X is a divalent group of the formula $>CHR^1$ or $>NR^1$,

R¹ is:

- 20 (A) a hydrogen atom,
- (B) alkyl of 1 to 2 carbon atoms which may be monosubstituted with:
- (i) oxo,
- (ii) aryl selected from the class consisting of phenyl or pyridyl,
wherein one hydrogen atom of said aryl group may be optionally
replaced with:
- (a) alkyl of 1 to 3 carbon atoms,
- (b) -COOH,
- (c) -SO₂OH,
- (d) -PO(OH)₂,
- 25 (e) a group of the formula $-OR^{12a}$, wherein R^{12a} is a hydrogen atom or a methyl, or

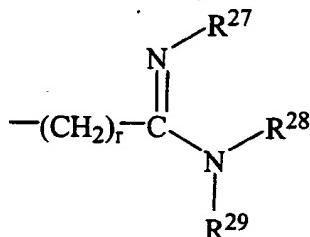
(f) an amidino group of the formula



wherein R¹³, R¹⁴ and R¹⁵ are each hydrogen atoms, or

5 (iii) a group of the formula -OR¹⁹, wherein R¹⁹ is a hydrogen atom or methyl,

- (C) a branched or unbranched carboxylic acid group of 3 to 6 carbon atoms,
- (D) a branched or unbranched phosphonic acid group of 2 to 6 carbon atoms,
- (E) a branched or unbranched sulfonic acid group of 2 to 6 carbon atoms,
- (F) an amidino group of the formula

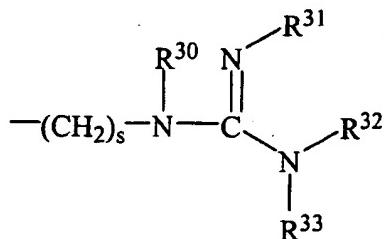


10

wherein r is 2, 3, 4, 5 or 6, and

R²⁷, R²⁸ and R²⁹ are each hydrogen atoms, or

- (G) an guanidino group of the formula



15

wherein s is 2, 3, 4, 5 or 6,

R³⁰, R³¹, R³² and R³³ are each hydrogen atoms,

R² is:

- (A) a hydrogen atom, or

(B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

5 phenyl

wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

(A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl,

10 wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

(i) methyl,

(ii) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,

15 (iii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl, or

(iv) halogen,

(B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R⁶²,

20 (C) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,

(D) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or R⁶²,

(E) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,

25 (F) cyano,

(G) nitro, or

(H) halogen;

R⁴ is Cl or trifluoromethyl;

30 R⁵ is a hydrogen atom; and,

R⁶ is CN or NO₂;

or a pharmaceutically acceptable salt thereof.

7. A compound of the formula I, in accordance with claim 1, wherein:

5 Y is an oxygen atom;

Z is an oxygen atom;

X is a divalent group of the formula >NR¹,

R¹ is:

(A) a hydrogen atom,

10 (B) methyl or ethyl, or

(C) -COCH₃

R² is:

(A) a hydrogen atom, or

15 (B) methyl;

R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

phenyl

20 wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

(A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl,

wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:

(i) methyl,

(ii) a group of the formula -COOR⁶³, wherein R⁶³ is methyl,

(iii) a group of the formula -OR⁶⁸, wherein R⁶⁸ is a hydrogen atom or methyl, or

(iv) halogen,

- (B) methyl, which may be mono- or polysubstituted with fluorine atoms or which may be monosubstituted with R⁶²;
- (C) a group of the formula -COOR⁷³, wherein R⁷³ is methyl,
- (D) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or R⁶²,
- 5 (E) a group of the formula -OR⁷⁹, wherein R⁷⁹ is a hydrogen atom, methyl or R⁶²,
- (F) cyano,
- (G) nitro, or
- 10 (H) halogen;

R⁴ is Cl or trifluoromethyl;
R⁵ is a hydrogen atom; and,
R⁶ is CN or NO₂;
15 or a pharmaceutically acceptable salt thereof.

8. A compound of the formula I, in accordance with claim 1, wherein:
Y is an oxygen atom;
- 20 Z is an oxygen atom;
X is a divalent group of the formula >NR¹,
- R¹ is:
- (A) a hydrogen atom,
- (B) methyl or ethyl, or
- 25 (C) -COCH₃

R² is:

(A) a hydrogen atom, or

(B) methyl;

30 R³ is a group of the formula -CH₂R⁴¹, wherein

R⁴¹ is

phenyl

wherein one or more of the hydrogen atoms of said phenyl group are necessarily and independently replaced with:

- 5 (A) R⁶², which is aryl selected from the class consisting of phenyl, or pyridyl,
 wherein one or more of the hydrogen atoms of said aryl group may be optionally and independently replaced with:
 (ii) methyl, or
10 (ii) halogen,
- (B) methyl, which may be mono- or polysubstituted with fluorine atoms,
- (C) a group of the formula -COR⁷⁸, wherein R⁷⁸ is methyl or R⁶²,
- 15 (D) halogen;

R⁴ is a chlorine atom;

R⁵ is a hydrogen atom; and,

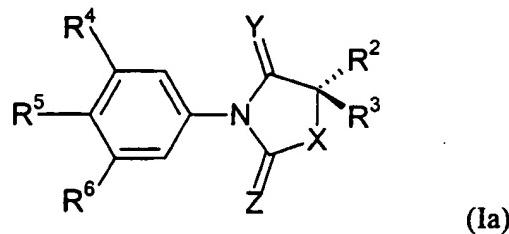
R⁶ is CN or NO₂;

20 or a pharmaceutically acceptable salt thereof.

9. A compound of the formula I, in accordance with claim 1, selected from the group consisting of:

25 5-(R)-(4-bromobenzyl)-3-(3-chloro-5-nitrophenyl)-5-methylimidazoline-2,4-dione; and,
 5-(R)-(4-bromobenzyl)-3-(3-chloro-5-cyanophenyl)-5-methylimidazoline-2,4-dione;
 or a pharmaceutically acceptable salt thereof.

30 10. A compound of the formula I, in accordance with claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 having the absolute stereochemistry depicted below in formula Ia.



11. A method for the treatment or prophylaxis of inflammatory or immune cell-mediated diseases which comprises administering to a host in need of such treatment or prophylaxis a therapeutic or prophylactic amount of a compound of the formula I in accordance with claim 1, 2, 3, 4, 5, 6, 7, 8 or 9.
- 10 12. The method of claim 11 wherein the disease or condition is selected from the group consisting of adult respiratory distress syndrome, shock, oxygen toxicity, multiple organ injury syndrome secondary to septicemia, multiple organ injury syndrome secondary to trauma, reperfusion injury of tissue due to cardiopulmonary bypass, myocardial infarction or use with thrombolysis agents, acute glomerulonephritis, vasculitis, reactive arthritis, 15 dermatosis with acute inflammatory components, stroke, thermal injury, hemodialysis, leukapheresis, ulcerative colitis, necrotizing enterocolitis and granulocyte transfusion associated syndrome.
- 20 13. The method of claim 11 wherein the disease or condition is selected from the group consisting of psoriasis, organ/tissue transplant rejection, graft vs. host reactions and autoimmune diseases including Raynaud's syndrome, autoimmune thyroiditis, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis; and systemic 25 lupus erythematosus.
14. The method of claim 11 wherein the disease or condition is asthma.

15. The method of claim 11 wherein the condition is toxicity associated with cytokine therapy.

5

16. A pharmaceutical composition comprising a compound of the formula I, in accordance with claim 1, 2, 3, 4, 5, 6, 7, 8 or 9.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/17712

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/4164, 31/4166; C07D 233/76, 233/84, 233/86
 US CL : 514/391; 548/318.1, 320.5, 321.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/391; 548/318.1, 320.5, 321.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 51-88631 B (SUMITOMO CHEMICAL CO., LTD.) 03 August 1976 (03.08.76), Compound Nos. 1-5, 15 and 16.	1-10

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

17 August 2000 (17.08.2000)

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